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Biomarkers

Prognostic Performance of Multiple Biomarkers in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

Analysis From the MERLIN–TIMI 36 Trial (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36)

Ryan G. O'Malley, MD,* Marc P. Bonaca, MD,*† Benjamin M. Scirica, MD, MPH,*† Sabina A. Murphy, MPH,* Petr Jarolim, MD, PhD,‡ Marc S. Sabatine, MD, MPH,*† Eugene Braunwald, MD,*† David A. Morrow, MD, MPH*†

Boston, Massachusetts

Objectives The aim of this study was to assess the prognostic performance of C-terminal provasopressin (copeptin), midregional pro-adrenomedullin (MR-proADM), and midregional pro-atrial natriuretic peptide (MR-proANP) in a large prospective cohort of patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS).

Background Copeptin, MR-proADM, and MR-proANP are emerging biomarkers of hemodynamic stress that have been associated with adverse cardiovascular (CV) outcomes in heart failure (HF) and stable ischemic disease.

Methods We measured copeptin, MR-proADM, and MR-proANP concentrations in 4,432 patients with NSTE-ACS who were randomized to treatment with ranolazine or placebo in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial and followed up for 1 year.

Results A high concentration (quartile 4 vs. quartiles 1 to 3) of each biomarker identified an increased risk of CV death or HF (copeptin: 13.2% vs. 5.0%, $p > 0.001$; MR-proADM: 15.8% vs. 4.1%, $p > 0.001$; MR-proANP: 17.7% vs. 3.5%, $p > 0.001$) as well as CV death, HF, and myocardial infarction individually (all $p \leq 0.001$). After adjustment for important covariates, each biomarker remained associated with CV death or HF at 1 year (adjusted hazard ratio: copeptin, 1.71; MR-proADM, 1.96; MR-proANP, 2.20; all $p \leq 0.001$). These biomarkers improved prognostic discrimination and patient reclassification for CV death or HF at 1 year (all categorical net reclassification improvement: <10%; $p > 0.001$) and maintained an independent association with composite CV death or HF when concurrently assessed in a model with clinical indicators plus B-type natriuretic peptide, cardiac troponin I, ST2, pregnancy-associated plasma protein A, and myeloperoxidase (each $p \leq 0.01$).

Conclusions Copeptin, MR-proADM, and MR-proANP are complementary prognostic markers for CV death and HF in patients with NSTE-ACS that perform as well as or better than established and other emerging biomarkers and warrant further investigation of application for therapeutic decision making. (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes; NCT00099788) (J Am Coll Cardiol 2014;63:1644–53)

From the *TIMI Study Group, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; †Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the ‡Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. The MERLIN–TIMI 36 trial was funded by CV Therapeutics. The testing of copeptin, MR-proADM, and MR-proANP was supported by Brahms Thermo Fisher. The TIMI Study Group has received research support from Abbott Laboratories, Accumetrics, Amgen, AstraZeneca, Athera, Bayer HealthCare, Beckman Coulter, BG Medicine, Biosite, Brahms, Bristol-Myers Squibb, Buhlmann Laboratories, Critical Diagnostics, CV Therapeutics, Daiichi Sankyo, Eisai, Eli Lilly and Co., GlaxoSmithKline, Integrated Therapeutics, Johnson & Johnson, Merck & Co., Inc., Millennium Pharmaceuticals, Nanosphere, Novartis Pharmaceuticals, Nuvelo, Ortho Clinical Diagnostics, Pfizer Inc., Randox, Roche Diagnostics, sanofi-aventis, sanofi-synthelabo, Schering-Plough, Siemens, and Singulex. Dr. Bonaca is an investigator with the TIMI Study Group and receives salary support from TIMI; and has served as a consultant for Roche Diagnostics. Dr. Scirica has received research grants via the TIMI Study Group and Brigham and Women's Hospital from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Johnson & Johnson, Bayer HealthCare, Gilead Sciences, Eisai, and Merck & Co., Inc.; and has served as a consultant for Lexicon, Arena, Gilead Sciences, Eisai, St. Jude's Medical, Forest Pharmaceuticals, Bristol-Myers Squibb, Boston Clinical Research Institute, Decision Resources, University of

Timely and accurate risk stratification is a central goal for the evaluation of patients with acute coronary syndrome (ACS) (1). Cardiac biomarkers, such as cardiac troponin (cTn), have proven useful when added to clinical risk indicators to better identify patients at risk for poor outcomes and, in some cases, to guide therapy (1). Although the proliferation of candidate biomarkers in recent years has been remarkable, few have convincingly improved upon discrimination of risk when added to established clinical tools (2). However, biomarkers of hemodynamic stress have emerged to be particularly strong and potentially useful prognostic indicators in patients with cardiovascular (CV) disease (3).

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C-terminal provasopressin (copeptin), midregional pro-adrenomedullin (MR-proADM), and midregional pro-atrial natriuretic peptide (MR-proANP) are emerging biomarkers of hemodynamic stress that are strongly predictive of poor outcomes in patients with heart failure (HF) (4–6). Pre-provasopressin is synthesized by the hypothalamus, and its stable C-terminal fragment, copeptin, is secreted by the pituitary gland in equimolar amounts to the less stable, physiologically active N-terminal peptide, arginine vasopressin (AVP), which acts to increase peripheral vascular resistance and stimulate reuptake of free water (7,8). AVP is eliminated from the circulation within minutes, whereas copeptin is stable for days and serves as a surrogate for measurement of AVP. MR-proADM is the stable portion of the prohormone of adrenomedullin, which is released primarily from the adrenal medulla, and is a potent vasodilator that also influences cardiac contractility, diuresis, and natriuresis (9,10). MR-proANP, the midregional epitope of the prohormone of atrial natriuretic peptide (ANP), stimulates vasodilation, natriuresis, and diuresis, similar to other natriuretic peptides. We recently reported an independent association of these biomarkers with CV outcomes in patients with stable ischemic heart disease (11), and several small studies have indicated that these biomarkers are promising for improving risk assessment in patients with unstable ischemic heart disease (4,7,10,12).

Therefore, we investigated the prognostic performance of these 3 emerging biomarkers of hemodynamic stress (copeptin, MR-proADM, and MR-proANP) in a large, well-characterized cohort of patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) as well as the relative and incremental prognostic value of these biomarkers concurrent with traditional clinical risk indicators and a broad panel of established and emerging biomarkers, including B-type natriuretic peptide (BNP), cTnI, pregnancy-associated plasma protein-A (PAPP-A), ST2, and myeloperoxidase (MPO).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
ANP = atrial natriuretic peptide
AVP = arginine vasopressin
BNP = B-type natriuretic peptide
CAD = coronary artery disease
copeptin = C-terminal provasopressin
cTn = cardiac troponin
CV = cardiovascular
HF = heart failure
HR = hazard ratio
IDI = integrated discrimination improvement
MI = myocardial infarction
MPO = myeloperoxidase
MR-proADM = midregional pro-adrenomedullin
MR-proANP = midregional pro-atrial natriuretic peptide
NRI = net reclassification improvement
NSTE-ACS = non–ST-segment elevation acute coronary syndrome
PPAP-A = pregnancy-associated plasma protein-A
TIMI = Thrombolysis In Myocardial Infarction

Methods

Patient population. The design and primary results of the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial have been reported previously (13). Patients eligible for enrollment had at least 10 min of ischemic symptoms at rest and presented with 1 of the following additional risk indicators: elevated levels of biomarkers of myonecrosis, ST-segment depression $\geq$0.1 mV, a history of diabetes mellitus, or an intermediate to high ($\geq$3) Thrombolysis In Myocardial Infarction (TIMI) risk score. Patients were excluded if they had end-stage renal disease requiring dialysis, cardiogenic shock, or a life expectancy <1 year. Patients were randomized in a 1:1 ratio to receive ranolazine or placebo. The protocol (including the biomarker substudy) was approved by the institutional review boards, and written consent was obtained from all patients.

Biomarker testing. The protocol specified that blood samples were to be obtained at enrollment in serum separator and ethylenediaminetetraacetic acid–anticoagulated plastic tubes, and serum and plasma were isolated within 60 min of sample acquisition. Samples were stored in plastic cryovials at −20°C or colder at the enrolling site until shipped to the TIMI Clinical Trials Laboratory (Boston, Massachusetts), where they were maintained at −80°C or colder.

Copeptin, MR-proADM, and MR-proANP were measured in plasma using the Kryptor Compact

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