8-21-2020

Biomarkers Enhance Discrimination and Prognosis of Type 2 Myocardial Infarction

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Recommended Citation

Horiuchi Y, Wettersten N, Patel MP, Mueller C, Neath S, Christenson RH, Morgenthaler NG, McCord J, Nowak RM, Vilke GM, Daniels LB, Hollander JE, Apple FS, Cannon CM, Nagurney JT, Schreiber D, deFilippi C, Hogan C, Diercks DB, Headden G, Limkakeng AT, Anand I, Wu AH, Ebmeyer S, Jaffe AS, Peacock W, Maisel AS. Biomarkers Enhance Discrimination and Prognosis of Type 2 Myocardial Infarction. Circulation 2020; .

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Yu Horiuchi, Nicholas Wettersten, Mitul P. Patel, Christian Mueller, Sean-Xavier Neath, Robert H. Christenson, Nils G. Morgenthaler, James McCord, Richard M. Nowak, Gary M. Vilke, Lori B. Daniels, Judd E. Hollander, Fred S. Apple, Chad M. Cannon, John T. Nagurney, Donald Schreiber, Christopher deFilippi, Christopher Hogan, Deborah B. Diercks, Gary Headden, Alexander T. Limkakeng, Inder Anand, Alan H.B Wu, Stefan Ebmeyer, Allan S. Jaffe, W. Frank Peacock, and Alan S. Maisel

10.1161/CIRCULATIONAHA.120.046682

Biomarkers Enhance Discrimination and Prognosis of Type 2 Myocardial Infarction

Running Title: *Horiuchi, et al.; Type 1 and 2 Myocardial Infarction and Biomarkers*

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This manuscript was sent to Prof. Harvey D. White, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Abstract

Background: The observed incidence of type 2 myocardial infarction (T2MI) is expected to increase with the implementation of increasingly sensitive cardiac troponin (cTn) assays. However, it remains to be determined how to diagnose, risk stratify and treat patients with T2MI. We aimed to discriminate and risk-stratify T2MI using biomarkers.
Methods: Patients presenting to the Emergency Department with chest pain, enrolled in the CHOPIN study, were retrospectively analyzed. Two cardiologists adjudicated type 1 MI (T1MI) and T2MI. The prognostic ability of several biomarkers alone or in combination to discriminate T2MI from T1MI was investigated using receiver operating characteristic (ROC) curve analysis. The biomarkers analyzed were cTnI, copeptin, mid-regional pro-atrial natriuretic peptide (MR-proANP), C-terminal pro-endothelin-1 (CT-proET1), mid-regional pro-adrenomedullin (MR-proADM) and procalcitonin. Prognostic utility of these biomarkers for all-cause mortality and major adverse cardiovascular event (MACE: a composite of acute MI, unstable angina pectoris, reinfarction, heart failure, and stroke) at 180-day follow-up was also investigated.
Results: Among the 2071 patients, T1MI and T2MI were adjudicated in 94 and 176 patients, respectively. Patients with T1MI had higher levels of baseline cTnI, while those with T2MI had higher baseline levels of MR-proANP, CT-proET1, MR-proADM, and procalcitonin. The area under the ROC curve (AUC) for the diagnosis of T2MI was higher for CT-proET1, MR-proADM and MR-proANP (0.765, 0.750, and 0.733, respectively) than for cTnI (0.631). Combining all biomarkers resulted in a similar accuracy to a model using clinical variables and cTnI (0.854 versus 0.884, p = 0.294). Addition of biomarkers to the clinical model yielded the highest AUC (0.917). Other biomarkers, but not cTnI, were associated with mortality and MACE at 180-day among all patients, with no interaction between the diagnosis of T1MI or T2MI.
Conclusions: Assessment of biomarkers reflecting pathophysiologic processes occurring with T2MI might help differentiate it from T1MI. Additionally, all biomarkers measured, except cTnI, were significant predictors of prognosis, regardless of type of MI.

Key Words: Type 2 myocardial infarction; Troponin; Biomarker; Diagnosis; Prognosis

Non-standard Abbreviations and Acronyms:
ACS: acute coronary syndrome
AF: atrial fibrillation
AMI: acute myocardial infacrction
AUC: area under the receiver operating characteristic curve
BNP: B-type natriuretic peptide
CAD: coronary artery disease
CHOPIN: Copeptin Helps in the early detection Of Patients with acute myocardial INfarction
cTn: cardiac troponin
CT-proET1: C-terminal pro-endothelin-1
ED: emergency department
HF: heart failure
IDI: integrated discrimination improvement
MACE: major adverse cardiovascular events
MR-proADM: Mid-regional pro-adrenomedullin
MR-proANP: Mid-regional pro-atrial natriuretic peptide

NRI: net reclassification improvement
PCI: percutaneous coronary intervention
ROC: receiver operating characteristic
T1MI: type 1 myocardial infarction
T2MI: type 2 myocardial infarction
UAP: unstable angina pectoris
VIF: variance inflation factor

Clinical Perspective

What is new?

- Patients with type 2 myocardial infarction (T2MI) had significant differences in a biomarker profile that had better diagnostic performance for discriminating T2MI from type 1 MI (T1MI) than cardiac troponin.
- T2MI was associated with higher admission levels of mid-regional pro-atrial natriuretic peptide, C-terminal pro-endothelin-1, mid-regional pro-adrenomedullin and procalcitonin.
- These biomarkers improved the prediction for T2MI with clinical variables and cardiac troponin.

What are the clinical implications?

- With further study, assessment of multiple biomarkers reflecting different pathophysiologic processes occurring with T2MI might help differentiate it from T1MI.

Introduction

Increasing recognition of the importance of the adverse prognostic implications of type 2 myocardial infarction (T2MI) have led to growing interest to better understand and diagnose this condition [1-7] . While type 1 MI (T1MI) results from acute atherothrombotic occlusion of a coronary vessel, T2MI results from myocardial oxygen supply/demand mismatch, which can occur with or without obstructive coronary artery disease (CAD) [8]. Both conditions lead to myocardial ischemia and injury resulting in release of cardiac troponin (cTn), the key diagnostic criteria for MI [8] . Although the prevalence of T2MI varies in the literature, the observed incidence of T2MI is expected to increase with the implementation of increasingly sensitive cTn assays because of their ability to detect smaller cTn increases more often seen in T2MI [1, 4, 7, 9, 10]. However, no official consensus exists for diagnosing, risk stratifying and treating this growing patient population who suffer a worse prognosis than those with T1MI [1-7, 11]. Currently, clinicians attempt to discriminate these two conditions by integrating multiple different pieces of data to determine the next best course of action. However, an incorrect diagnosis could lead to adverse outcomes such as complications of T1MI, unnecessary testing, or harms from incorrect therapies. Thus, tools to help discriminate T1MI and T2MI and the underlying causes of T2MI to guide a potential treatment strategy are urgently needed.

Several studies have reported that a combination of clinical information and levels of cTnI can help differentiate T2MI from T1MI [4, 12, 13]. However, the use of other clinically available biomarkers that reflect potential pathophysiologic causes of T2MI has not been fully investigated. Since acute stressors provoking oxygen supply/demand mismatch in T2MI may be multifactorial from conditions such as hypotension, shock, respiratory failure, anemia, tachyarrhythmia and hypertension with or without left ventricular hypertrophy, biomarkers may provide an opportune method to evaluate these diverse pathophysiologic processes [8]. The

Copeptin Helps in the early detection Of Patients with acute myocardial INfarction (CHOPIN) study was a multicenter international cohort study of patients presenting to the Emergency Department (ED) with chest pain, and evaluated multiple biomarkers which can be reflective of these acute conditions [14].

Copeptin is a stable surrogate for arginine vasopressin and responds rapidly to the acute stressors releasing adrenocorticotropic hormone and cortisol [15, 16]. Mid-regional pro-atrial natriuretic peptide (MR-proANP) reflects atrial wall stretch and is a marker of volume overload [17]. C-terminal pro-endothelin-1 (CT-proET1) is a vasoactive agent and regulates multiple cardiovascular conditions such as myocardial hypertrophy, arrythmia and volume retention [18]. MR-proANP and CT-proET1 are also related to atrial fibrillation (AF), which can precipitate T2MI with tachycardia and bradycardia [19, 20]. Mid-regional pro-adrenomedullin (MR-proADM) is released by a variety of stimuli such as ventricular volume overload and sepsis [21, 22]. Procalcitonin is a well-known biomarker for bacterial infection [23]. Therefore, many of these biomarkers can be associated with acute conditions and stressors that could cause a T2MI and therefore may help with diagnosis and prognosis. Furthermore, biomarkers that can predict T2MI may also provide insight into the pathophysiologic processes driving T2MI allowing clinicians to determine a potential treatment strategy. In this analysis, we aimed to investigate the (1) characteristics of biomarker profiles in patients with T2MI, (2) clinical characteristics and biomarkers useful for differentiating T2MI from T1MI, and (3) prognostic implication of biomarkers in patients with T2MI.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and population

The CHOPIN study was a prospective, multicenter, international cohort study that enrolled patients who presented to the ED with chest pain or its related symptoms within 6 hours of symptom onset [14]. Patients with symptoms which were clearly not from acute coronary syndrome (ACS) were excluded. The study was conducted in accordance with international conference on harmonization/good clinical practice regulations and was approved by the institutional review committee at each participating center. All patients provided written informed consent for participation.

Detailed clinical information was recorded including demographics, vital signs, symptoms at presentation, physical examination findings, past medical history, medications at home and discharge, laboratory data, electrocardiogram, echocardiogram, chest X-ray, stress testing (either exercise or pharmacologic and either echocardiogram, nuclear or magnetic resonance imaging), coronary angiography, percutaneous coronary intervention (PCI) and coronary bypass surgery.

Blood samples were obtained at the time of presentation (0 hour; baseline value) and 2, 6, 24 and 72 hours later. For this study, we focused on samples collected at presentation as it would be most informative to a treating physician to be able to discriminate T2MI from T1MI as early as possible as well as this had the highest rate of collection. The blood was centrifuged, and plasma was stored frozen at -60°C or colder for the analysis in the core laboratory. cTnI was measured with the contemporary cTnI Ultra assay on an ADVIA Centaur XP system (Siemens Healthcare Diagnostics, Norwood, Massachusetts). The assay detection limit was 0.006 μg/l, the 99th percentile was 0.040 μg/l, and a 10% coefficient of variation was at 0.030 μg/l. Other biomarkers included copeptin, MR-proANP, CT-proET1, MR-proADM and procalcitonin. These biomarkers were measured in the core laboratory on a Kryptor Compact platform (BRAHMS

GmbH, Hennigsdorf, Germany, Supplemental Table I).

Adjudication of T1MI and T2MI

A total of 2,071 patients were enrolled with 63 patients presenting > 6 hours after symptom onset subsequently excluded. Of the remaining 2008 patients, 303 patients who had a rise and/or fall of cTnI with at least one value above the 99th percentile, as per recommendations of the 4th universal definition of MI, were considered for adjudication for T1MI and T2MI [8]. A rise or fall was considered significant if there was a change > 20%. Two independent cardiologists (A.M. and M.P.) reviewed each case and decided the final adjudication of T1MI, T2MI or unclassified. Patients who did not have either signs and/or symptoms of ischemia were excluded as non-acute MI (AMI) patients. For the adjudication of T2MI, a condition that could be attributed to provoking myocardial oxygen supply/demand imbalance was required. These included fixed coronary atherosclerosis without plaque rupture, coronary artery spasm, microvascular dysfunction, embolism and dissection, severe bradyarrhythmia, respiratory failure with severe hypoxemia, severe anemia, hypotension/shock, sustained tachyarrhythmia or severe hypertension with or without left ventricular hypertrophy, post-surgical status, sepsis, acute heart failure with sub endomyocardial ischemia, structural heart disease such as severe aortic stenosis and hypertrophic cardiomyopathy, and other possible contributors judged by the case reviewers [1-3, 8, 11]. In the event of disagreement, the two cardiologists discussed the case and determined the diagnosis or excluded the case as unclassified. Patient information reviewed included the clinical characteristics as well as cTnI values. Adjudicators were blinded to the levels of all biomarkers except cTnI. Additionally, they also reviewed the primary and secondary diagnosis in the original CHOPIN study (Supplemental Table II). These diagnoses were made by board certified cardiologists at each study institution after the completion of the 30-day follow-up.

Study endpoints

The clinical endpoints were 1) all-cause mortality and 2) major adverse cardiovascular events (MACE) within 180 days after initial presentation but not including the index presentation. MACE was defined as an ED visit and/or hospitalization for the following diagnoses: AMI, unstable angina pectoris (UAP), reinfarction, heart failure (HF), or stroke. Ischemic events (AMI, UAP, and reinfarction) and HF were also evaluated individually.

Statistical analysis

Continuous variables with normal distribution were described as means and standard deviations, and those with non-normal distribution were described as medians and 25^{th} and 75^{th} percentiles. Categorical variables were described as percentages. The t-test, Mann-Whitney and Chi-square tests were used as appropriate to compare the patient characteristics between patients with T1 and T2MI. Correlations of biomarkers were investigated with Spearman's rank correlation. Receiver operating characteristic (ROC) curve analysis was employed to investigate the usefulness of each biomarker and their combination for the diagnosis of T2MI. We created models using clinical characteristics and biomarkers for diagnosing T2MI from T1MI. First, we made a multivariable model with clinical variables and cTnI. Next, another biomarker was included in this model and its improvement was assessed with net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The final multivariable model explored all significant clinical variables and biomarkers (cTnI, copeptin, MRpro-ANP, CT-proET1, MR-proADM, and procalcitonin). Univariable logistic regression analysis was used to assess the association between each clinical characteristic and the diagnosis of T2MI. A stepwise multivariable model was built using potential predictors with a p-value < 0.05 in univariable analysis and were reduced using backward step-down selection with Akaike information criterion as the stopping rule. Variance inflation factor (VIF) was used to assess multicollinearity

in the multivariable model. The Kaplan-Meier analysis, log-rank test, and Cox regression analysis were used for mortality and MACE analysis. Because of the small number of events (23 death and 45 MACE), multivariable analysis was not performed. An interaction between T1MI/T2MI and levels of biomarkers on mortality and MACE was also investigated. All biomarkers were log-2 transformed in the logistic regression and Cox regression analysis. All statistical analyses were performed using R x64 3.6.3 for Windows.

Results

Among 303 patients considered for adjudication, 5 were diagnosed as not having AMI and 28 could not be classified as T1MI or T2MI. Of the remaining 270 (89%), 94 and 176 were diagnosed with T1MI and T2MI, respectively. Among possible contributors for T2MI, hypertension (38%) and tachyarrhythmia (24%) were leading causes and 23% was associated with fixed coronary artery disease (Supplemental Table III).

Patients with T2MI were more likely to be female and non-white, and more frequently had comorbidities such as hypertension, HF and AF compared to those with T1MI (Table 1). Patients with T2MI were more often previously treated with warfarin, diuretics, and digoxin. Those with T2MI were less likely to have the typical chest discomfort of pressure, heavy or radiation to the arm and shoulder, but more frequently had sharp chest discomfort. ST elevation MI was rare in T2MI. Patients with T2MI had higher heart rate, creatinine, B-type NP (BNP) and lower hemoglobin.

Patients with T1MI more frequently underwent invasive procedures including coronary angiography and PCI, while non-invasive stress testing was more often performed in those with T2MI (Supplemental Figure I). At discharge, patients with T1MI were more frequently treated with antiplatelet therapies, statins, beta-blockers, and angiotensin converting enzyme-inhibitors,

whereas warfarin and diuretics were more often prescribed in T2MI (Supplemental Table IV).

Patients with T1MI had higher levels of cTnI at presentation and with subsequent measurements (Figure 1). Levels of copeptin were higher in T2MI at 4th and 5th follow-up time points but not at earlier measurements. Levels of other biomarkers were higher in T2MI at presentation and follow-up. Spearman's rank correlation showed MR-proANP, CT-proET1 and MR-proADM were strongly correlated ($r = 0.730$ for MR-proANP and CT-proET1, $r = 0.700$ for MR-proANP and MR-proADM, and $r = 0.900$ for CT-proET1 and MR-proADM, $p < 0.001$ for all, Supplemental Table V).

At 180-day follow up, 23 of 270 patients died (8.5%) and 45 had MACE (17%; AMI in 11, UAP in 7, reinfarction in 4, HF in 25, and stroke in 3 patients). Mortality was similar between T1MI and T2MI, and patients with T2MI more frequently had MACE (Figure 2). The incidence of HF events was significantly higher, and ischemic events was numerically higher in patients with T2MI (ischemic events, 5.3% in T1MI versus 10% in T2MI, $p = 0.200$; HF events, 0% versus 14%, $p < 0.001$).

For diagnosing T2MI, CT-proET1, MR-proADM and MR-proANP had better area under the ROC curves (AUCs) than cTnI (0.765, 0.750, 0.733 and 0.631, respectively, Table 2 and Figure 3). Combining all biomarkers resulted in an AUC of 0.854 (model 1, Table 2 and Supplemental Table VI). Clinical characteristics included in a multivariable model with cTnI (model 2) were sex, race, AF, warfarin, location of pain (chest), ST elevations, heart rate, bilateral rales and creatainine with an AUC of 0.884 (Table 2 and Supplemental Table VI), which was not statistically higher than the biomarker model ($p = 0.294$). The addition of copeptin to this model significantly improved discrimination by both NRI and IDI (Supplemental Table VII). In the stepwise model combining clinical characteristics and all biomarkers (model 3), factors included in the final model were race, warfarin, chest discomfort (pressure and heavy), location

of pain (chest), ST elevations, heart rate, creatinine, cTnI, copeptin, CT-proET1, MR-proADM, and procalcitonin (Table 2 and Supplemental Table VI). The AUC of this model was 0.917, which was significantly higher than model 1 and 2 ($p < 0.001$ and $p = 0.026$, respectively). Considering the strong correlation between CT-proET1 and MR-proADM and the relatively high VIFs in the multivariable models suggesting collinearity with these two biomarkers in the model, we tested the model by removing one of these two biomarkers, which resulted in a similar selection of variables and AUCs (0.919 for model without CT-proET1 and 0.912 for model without MR-proADM). A similar finding was observed when patients who were not adjudicated as either T1 or T2MI were included as unclassified patients in the study population and models were made for diagnosing T2MI (Supplemental Table VIII, IX and X and Supplemental Figure II).

When evaluating the prognostic utility of biomarkers, all biomarkers other than cTnI were prognostic for 180-day mortality, a finding not influenced by the diagnosis of T1MI or T2MI (Table 3 and Figure 4A). Similarly, biomarkers other than cTnI and copeptin were predictive of 180-day MACE with no interaction by T1MI or T2MI diagnosis (Figure 4B). None of the biomarkers predicted ischemic events (Figure 4C), but MR-proANP, CT-proET1, MR-proADM, and procalcitonin were significant predictors of HF events. No HF events were observed in patients with T1MI and an interaction analysis for HF events was not conducted (Figure 4D).

Discussion

In this post-hoc analysis of the CHOPIN study, we demonstrated that patients with T2MI had significant differences in a biomarker profile that had better diagnostic performance for discriminating T2MI from T1MI than cTnI. The use of six biomarkers together had a similar

diagnostic accuracy to a model that included nine different clinical characteristics plus cTnI. Furthermore, the accuracy of these models improved when both clinical characteristics and biomarkers were considered with an AUC of 0.917. Additionally, biomarkers except cTnI were predictive of mortality and MACE at 180-day and this was not influenced by the diagnosis of T1MI or T2MI.

In our study of 2008 patients presenting to the ED with chest pain, we found 176 (8.8%) had T2MI. The reported incidence of T2MI is highly variable (ranging from 3 to 17%) [4, 7, 10, 24-27]. Studies with low reported incidences screened all patients presented to the ED or enrolled patients with cTnI measurements regardless of the presence of ischemic relevant symptoms [24, 25]. Those that focused on more high-risk patients for ACS, such as CHOPIN, reported higher incidences [4, 7, 10, 26, 27]. These differences can be due to heterogeneous study populations, differences in indication for cTn measurement, a lack of definitive diagnostic criteria, and variations in the adjudication process with varied observed incidence of T1MI and myocardial injury. In our analysis, 417 patients had the peak cTnI above the 99th percentile. Of these, 270 patients were adjudicated either T1 or T2MI, thus the remaining 147 (35%) could have had myocardial injury. The incidence of myocardial injury among patients with elevated cTn also widely varies from 13 to 69% [1, 10, 11, 24-27]. Notably, few studies have evaluated how to discriminate acute myocardial injury from other causes of troponin elevation. Hartikainen et al. evaluated 2,302 patients presenting to the ED with symptoms suggestive of MI and adjudicated these patients according to the 4th definition of MI [26]. Among 1097 patients with cTn elevation, 78 patients (7.1%) had acute myocardial injury. Although our analysis focused on the differences between T1 and T2MI, future studies should also evaluate discriminating T1MI, T2MI and acute and chronic myocardial injury to better understand the spectrum of patients with cTn elevation. Our study also showed patients with T2MI had a similar mortality to those with T1MI while

suffering from a higher incidence of MACE. The non-significant difference in mortality analysis in our study needs to be interpreted cautiously considering the small number of deaths. T2MI has been generally associated with worse outcomes compared with T1MI, though previous studies have been inconsistent. Studies have reported various outcomes in mortality between T1MI and T2MI including a similar mortality between T1MI and T2MI, a similar crude mortality that then differs after adjustment of confounding factors, and also a higher non-cardiovascular mortality in T2MI [1-3, 6, 11, 12, 28]. Due to the wide variety of patient populations, characteristics and acute conditions that can present with T2MI, precise prognostication remains challenging.

Our study adds to the literature by providing novel insights for several of biomarkers that can evaluate different pathophysiologic processes involved in T2MI. Patients with T2MI had higher admission levels of MR-proANP, CT-proET1 and MR-proADM, which are reflective of volume overload and congestion. Notably, the reported prevalence of HF in T2MI patients is highly variable ranging between 16 to 37% [3-5, 12, 25, 28-30]. In our study, patients with T2MI more frequently had a history of HF (34%) and were associated with a higher incidence of HF events than those with T1MI. Given our high prevalence of HF, one may consider that many acute HF patients are misclassified as having T2MI; however, the CHOPIN study enriched for patients with possible ACS by requiring chest pain or an ischemic equivalent symptom to be present for inclusion. During our adjudication process, symptoms and/or signs of ischemia were required for adjudicating a troponin elevation as either T1 or T2MI and those without an ischemic finding were ruled out as myocardial injury. Among patients classified as T2MI in our analysis, 8% were adjudicated by ischemia due to increased transmural pressure with HF. The underlying disease processes for T2MI and HF frequently co-exist such as coronary artery disease, hypertension, left ventricular hypertrophy and anemia, and hemodynamic perturbations during an acute state, such as tachycardia, bradycardia, severe hypertension, hypotension, shock, and respiratory failure. HF

has been demonstrated as one of the leading triggering mechanism of T2MI and patients with T2MI were more frequently readmitted for HF events [4-6, 28]. Therefore, HF may serve as both the underlying cardiac disease and acute stressor in T2MI. MR-proANP, CT-proET1 and MR-proADM can reflect these varied hemodynamic stressors as a possible causes or contributors of T2MI. In addition, levels of MR-proANP and CT-proET1 are elevated in AF with atrial stress, which may induce T2MI with tachycardia and bradycardia [19, 20]. CT-proET1 is also associated with myocardial hypertrophy, arrhythmogenicity and increased contractility and renal aldosterone production [18]. Therefore, these biomarkers reflect states of congestion, vascular tone, neurohormonal activation and AF, which are frequently associated with T2MI.

Although the AUC of copeptin for predicting T2MI was small in our analysis, the model with clinical variables and cTnI improved with the addition of copeptin when assessed by NRI and IDI analyses. Copeptin had adjusted ORs of 0.59 and 0.51 with p-value < 0.001 in models with all biomarkers and with clinical variables and all biomarkers. Therefore, after adjustment for confounding factors, higher levels of copeptin indicated an improved prediction for T1MI. While levels of copeptin are known to be indicative of acute stress conditions, it is also secreted by baroreceptor stimulation from hypotension or direct damage to the cardiac baroreceptor [15, 16]. Therefore, after adjustment for baseline characteristics, T1MI may be associated with severe myocardial damage and a higher stress state than T2MI. This hypothesis is supported by significantly higher copeptin levels found in patients with STEMI compared to NSTEMI, and still higher in STEMI and NSTEMI than unstable angina [31]. Similarly, whereas patients with T2MI had higher levels of procalcitonin, its elevation was associated with a higher odds for T1MI in multivariable analysis. This may be because procalcitonin is also elevated in infection-independent cases such as AMI and cardiac shock [32, 33]. After adjustment for confounders, procalcitonin could predict more severe myocardial injury in T1MI.

cTnI is the principal biomarker for diagnosing AMI, but it is not able to distinguish the type of MI. Although it has been frequently reported that admission values of cTn are higher with T1MI than T2MI, levels vary widely and have significant overlap [4, 10, 12]. In a study that evaluated a high sensitivity cTn assay in 287 patients with T1MI and T2MI, patients with T2MI had lower levels of cTnI at admission, 1 hour, and 3 hours [12]. The AUC of baseline cTnI for diagnosing T2MI was 0.63 and improved to 0.71 in combination with age and radiating chest pain, which were significant predictors in a multivariable model. The low predictive ability of a single cTnI measurement, and its improvement with clinical characteristics, was also observed in our study. Our higher AUC compared to prior studies is likely due to the detailed clinical information considered in the multivariable model. While several of the biomarkers had a better AUC than cTnI, this was not the case in the multivariable model with clinical information and cTnI, suggesting that the underlying causes of T2MI are heterogeneous and are not explained by a single biomarker. Although combining only biomarkers had a high AUC (0.854), the model with clinical variables and cTnI showed a similar accuracy (0.884), which was significantly but only marginally improved to 0.917 when other biomarkers were included. This lack of marked change might be because clinical characteristics indicative of the pathophysiologic processes causing biomarker elevations were already included in the model. At this time, it is recommended to make use of detailed history, physical examination and standard laboratory testing for the diagnosis of T2MI. However, the weaknesses in this approach should also be recognized because these clinical findings can be more subjective and are at risk for disagreement in interpenetration by different physicians whereas biomarkers are more objective. To this point, Gard et al. reported symptoms of dyspnea, higher systolic blood pressure and C reactive protein levels were likely to lead to disagreement for the classification of T2MI [13]. With further studies, a panel of biomarkers that simplifies the integration of these multiple clinical

factors in a more objective manner may help better discrimination of T2MI.

Lastly, several studies have reported that patients with T2MI who had underlying CAD had a worse prognosis than those without CAD [2, 10, 12]. CAD may be underdiagnosed in patients with T2MI due to lower use of diagnostic testing, which may result in fewer patients discharged with revascularization and medications proven to improve outcomes in patients with CAD [28]. In our study, cTnI as well as other biomarkers were not associated with ischemic events. Currently, there is no established strategy for the assessment of possible CAD in patients with T2MI. Further studies are needed to determine who might benefit from the assessment and treatment of potential underlying CAD.

Limitations

Although two cardiologists adjudicated T1MI versus T2MI using detailed clinical information, potential misclassification may have occurred. There was no standardized approach to diagnose CAD and not all patients underwent imaging testing. The troponin assay used in this study was contemporary at the time of CHOPIN but newer-generation assays with better sensitivity are now available that may detect more cases of MI. Patients who were excluded as either T1MI or T2MI may have influenced the result, though results including these patients were comparable. BNP and N-terminal proBNP were not measured in the central laboratory and were recorded on admission in 41% and 12% of patients, respectively; therefore, we included MR-proANP in the models instead of BNPs which has comparable diagnostic value and was measured in everyone. Even though this is a unique dataset with multiple biomarker measurements, the number of study population and clinical events were relatively small. The non-significant differences for mortality and interaction analyses need to be interpreted cautiously. Our results could not be validated in another cohort given the distinctive biomarker measurements performed in CHOPIN. Furthermore, internal validation with splitting the dataset was not performed due to the small

number of study population. Therefore, the risk of overfitting does exist and thus our results are only hypothesis generating and should be interpreted cautiously. Further study in alternative cohorts are needed to validate the findings of this study.

Conclusion

Among AMI patients presenting to the ED with chest pain, those with T2MI had a distinctive biomarker profile, which showed a better diagnostic performance than cTnI alone. These findings suggest biomarkers may help discriminate T2MI and T1MI, while further research is required to confirm our findings. Other biomarkers, but not cTnI, were predictive of mortality and MACE at 180-day among all patients and this did not interact with the diagnosis of T1MI and T2MI.

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Acknowledgments

None

Sources of Funding

This study uses data from the CHOPIN trial. BRAHMS GmbH (part of Thermo Fisher Scientific) financed the CHOPIN trial but did not provide funds for this study.

Disclosures

Dr. McCord has received research support from Roche, Siemens, Abbott and Beckman, and consultant fee from Roche and Siemens (all significant). Dr. Nowak has had grant support from Roche, Abbott, Siemens and Beckman and has had a modest relationship with these companies as far as consulting goes. Dr. Daniels has had Honoraria from Quidel (modest), Abbott

(significant), Janssen (significant) and Roche (significant), and had other research support from Critical Diagnostics (modest). Dr. Limkakeng has received significant research grants from Roche Diagnostics, Inc., Abbott Laboratories, Siemens Healthcare Diagnostics, Hospital Quality Foundation, Bristol Meyers Squibb Ischemia Care, LTD., GE, Astrazeneca and Forest Devices, Inc. Dr. Jaffe has consulted for Abbott, Siemens, Roche, Beckman-Coulter, ET Healthcare, Sphingotec, Quidel, Brava, Blade and Novartis. Dr. Peacock has had consultant fees from Abbott, Beckman, Ortho Clinical Diagnostics, Osler, Roche, Quidel and Siemens (all modest).

Supplemental Materials

Supplemental Figures I - II

Supplemental Tables I - X

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Table 1. Baseline Characteristics of Type 1 and Type 2 Myocardial Infarction Patients

	T1MI	T2MI	p-value
	n = 94	n = 176	
Age, years, mean (SD)	60 (11)	63 (13)	0.075
Male sex	**74 (78.7)**	**115 (65.3)**	**0.032**
White	**61 (64.9)**	**77 (43.8)**	**0.001**
Past Medical History			
CAD	47 (50.0)	94 (53.4)	0.684
Hypertension	**63 (67.0)**	**144 (81.8)**	**0.010**
Heart failure	**9 (9.6)**	**59 (33.5)**	**<0.001**
Dyslipidemia	57 (60.6)	105 (59.7)	0.979
Stroke	8 (8.5)	30 (17.0)	0.082
Diabetes Mellitus	33 (35.1)	69 (39.2)	0.596
Atrial fibrillation	**3 (3.2)**	**37 (21.0)**	**<0.001**
COPD	7 (7.4)	27 (15.3)	0.095
Smoking			0.761
current	34 (36.2)	58 (33.0)	
never	36 (38.3)	66 (37.5)	
past	24 (25.5)	52 (29.5)	
Medication prior to admission			
Aspirin	44 (46.8)	93 (52.8)	0.414
Clopidogrel	16 (17.0)	34 (19.3)	0.765
Warfarin	**1 (1.1)**	**28 (15.9)**	**<0.001**
Statins	41 (43.6)	90 (51.1)	0.294
Beta-blockers	35 (37.2)	86 (48.9)	0.089
ACE-inhibitors	35 (37.2)	85 (48.3)	0.107
Aldosterone inhibitors	0 (0)	1 (0.6)	1.000
Diuretics	**17 (18.1)**	**55 (31.2)**	**0.029**
Digoxin	**0 (0)**	**12 (6.8)**	**0.023**
Calcium channel blockers	8 (8.5)	31 (17.6)	0.065
Nitroglycerine	18 (19.4)	44 (25.3)	0.346
Clinical character at presentation			
Symptom onset, gradual	27 (28.7)	46 (26.1)	0.755
Symptoms occurrence, intermittent	40 (42.6)	66 (37.5)	0.497
Symptoms at presentation	80 (85.1)	135 (76.7)	0.140
Chest discomfort, pressure	**58 (61.7)**	**81 (46.0)**	**0.020**
Chest discomfort, heavy	**30 (31.9)**	**30 (17.0)**	**0.008**
Chest discomfort, sharp	**12 (12.8)**	**43 (24.4)**	**0.035**
Location of pain, chest	89 (94.7)	152 (86.4)	0.058
Location of pain, arm/shoulder	**34 (36.2)**	**38 (21.6)**	**0.015**
Location of pain, jaw/neck	16 (17.0)	18 (10.2)	0.158
Location of pain, epigastric	10 (10.6)	13 (7.4)	0.495
Symptom severity, (median [25th percentile, 75th percentile])	7.00 [4.00, 10.00]	6.00 [2.00, 8.00]	0.055
Symptom duration			0.681
< 2 minutes	2 (2.3)	6 (3.7)	
2-10 minutes	11 (12.6)	28 (17.4)	
10-30 minutes	14 (16.1)	26 (16.1)	
30 minutes	60 (69.0)	101 (62.7)	

ST elevation	**22 (23.4)**	**8 (4.5)**	**<0.001**
ST-T change	18 (19.1)	44 (25.0)	0.349
Systolic BP, mmHg, mean (SD)	144 (26)	146 (35)	0.683
Diastolic BP, mmHg, mean (SD)	83 (17)	82 (20)	0.707
Heart rate, beats/min, mean (SD)	**80 (17)**	**91 (27)**	**<0.001**
Bilateral rales	**3 (3.2)**	**21 (11.9)**	**0.029**
Wheezing	2 (2.1)	11 (6.2)	0.227
S3	3 (3.2)	13 (7.4)	0.263
Creatinine, mg/dl, median [25th percentile, 75th percentile]	**0.95 [0.79, 1.10]**	**1.20 [0.99, 1.91]**	**<0.001**
Hemoglobin, g/dl, median [25th percentile, 75th percentile]	**14.6 [13.0, 15.6]**	**12.9 [11.5, 14.3]**	**<0.001**
BNP, ng/l, median [25th percentile, 75th percentile]	**113 [33, 269]**	**305 [89, 1384]**	**0.008**
NT-proBNP, ng/l, median [25th percentile, 75th percentile]	104 [52, 2086]	2189 [931, 5900]	0.063

Data are expressed as n (%) for categorical variables.

ACE, angiotensin converting enzyme; BNP, B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro b-type natriuretic peptide; SD, standard deviation; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction

Table 2. Diagnostic Performance of Biomarkers for Diagnosis of Type 2 Myocardial Infarction

	AUC	95% CI
cTnI	0.631	0.553-0.709
Copeptin	0.501	0.423-0.579
MR-proANP	0.733	0.673-0.793
CT-proET1	0.765	0.707-0.822
MR-proADM	0.750	0.690-0.810
Procalcitonin	0.652	0.584-0.719
All biomarkers	0.854	0.802-0.905
Clinical variables and cTnI	0.884	0.843-0.925
Clinical variables and biomarkers	0.917	0.880-0.954

$p = 0.294$ for model with all biomarkers versus model with clinical variables and cTnI, $p < 0.001$ for model with all biomarkers versus model with clinical variables and biomarkers and $p = 0.026$ for model with clinical variables and cTnI versus model with clinical variables and biomarkers.
AUC, area under the receiver operating characteristics curve; CI, confidence interval; cTnI, cardiac troponin I; CT-proET1, C-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide

Table 3. Cox Regression Analysis for Clinical Outcomes

Mortality			
	HR	95% CI	p-value
cTnI	1.01	0.85-1.18	0.954
Copeptin	1.32	1.04-1.67	0.021
MR-proANP	1.41	1.09-1.83	0.010
CT-proET1	1.66	1.11-2.47	0.013
MR-proADM	1.86	1.30-2.66	0.001
Procalcitonin	1.32	1.04-1.69	0.024
MACE			
	OR	95% CI	p-value
cTnI	1.05	0.94-1.17	0.398
Copeptin	1.04	0.88-1.22	0.669
MR-proANP	1.49	1.24-1.79	< 0.001
CT-proET1	1.61	1.22-2.13	0.001
MR-proADM	1.51	1.17-1.96	0.002
Procalcitonin	1.31	1.10-1.55	0.002
Ischemic Events			
	OR	95% CI	p-value
cTnI	1.00	0.85-1.18	0.971
Copeptin	0.95	0.74-1.22	0.682
MR-proANP	1.23	0.95-1.59	0.112
CT-proET1	1.16	0.76-1.76	0.485
MR-proADM	1.27	0.86-1.88	0.230
Procalcitonin	1.16	0.89-1.52	0.277
Heart Failure Event			
	OR	95% CI	p-value
cTnI	1.03	0.89-1.19	0.722
Copeptin	1.20	0.97-1.48	0.088
MR-proANP	1.99	1.52-2.59	< 0.001
CT-proET1	2.36	1.64-3.41	< 0.001
MR-proADM	2.01	1.45-2.79	< 0.001
Procalcitonin	1.49	1.21-1.83	< 0.001

All biomarkers were log-2 transformed. CI, confidence interval; cTnI, cardiac troponin I; CT-proET1, C-terminal pro-endothelin-1; HR, hazard ratio; MACE, major adverse cardiovascular events; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide

Figure Legends

Figure 1. Levels of Biomarkers in Patients with Type 1 and 2 Myocardial Infarction.

†: $p < 0.05$

Upper and lower box show 1st and 3rd quartiles. Middle line shows the median value.

Upper whisker limit = 3rd quartile + 1.5*inter quartile range. Lower whisker limit = 1st quartile – 1.5 * inter quartile range.

cTnI, cardiac troponin I; CT-proET1, C-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide, T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction

Figure 2. 180-day Outcomes in Patients with Type 1 and 2 Myocardial Infarction. Mortality was similar between T1MI and T2MI (Figure 2A). T2MI was associated with higher incidence of MACE (Figure 2B). MACE, major adverse cardiovascular events; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction

Figure 3. Receiver Operating Characteristic Curve Analysis for Diagnosing Type 2 Myocardial Infarction. AUC, area under the receiver operating characteristic curve; CI, confidence interval; cTnI, cardiac troponin I; CT-proET1, C-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide

Figure 4. Prognostication of Biomarkers for 180-day Outcomes. All biomarkers other than cTnI were prognostic for 180-day mortality, a finding not influenced by the diagnosis of T1MI or

T2MI (Figure 4A). Similarly, biomarkers other than cTnI and copeptin were predictive of 180-day MACE with no interaction by T1MI or T2MI (Figure 4B). None of the biomarkers predicted ischemic events (Figure 4C). No HF events were observed in patients with T1MI and an interaction analysis for HF events was not conducted (Figure 4D). All biomarkers were log-2 transformed.

cTnI, cardiac troponin I; CT-proET1, C-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide

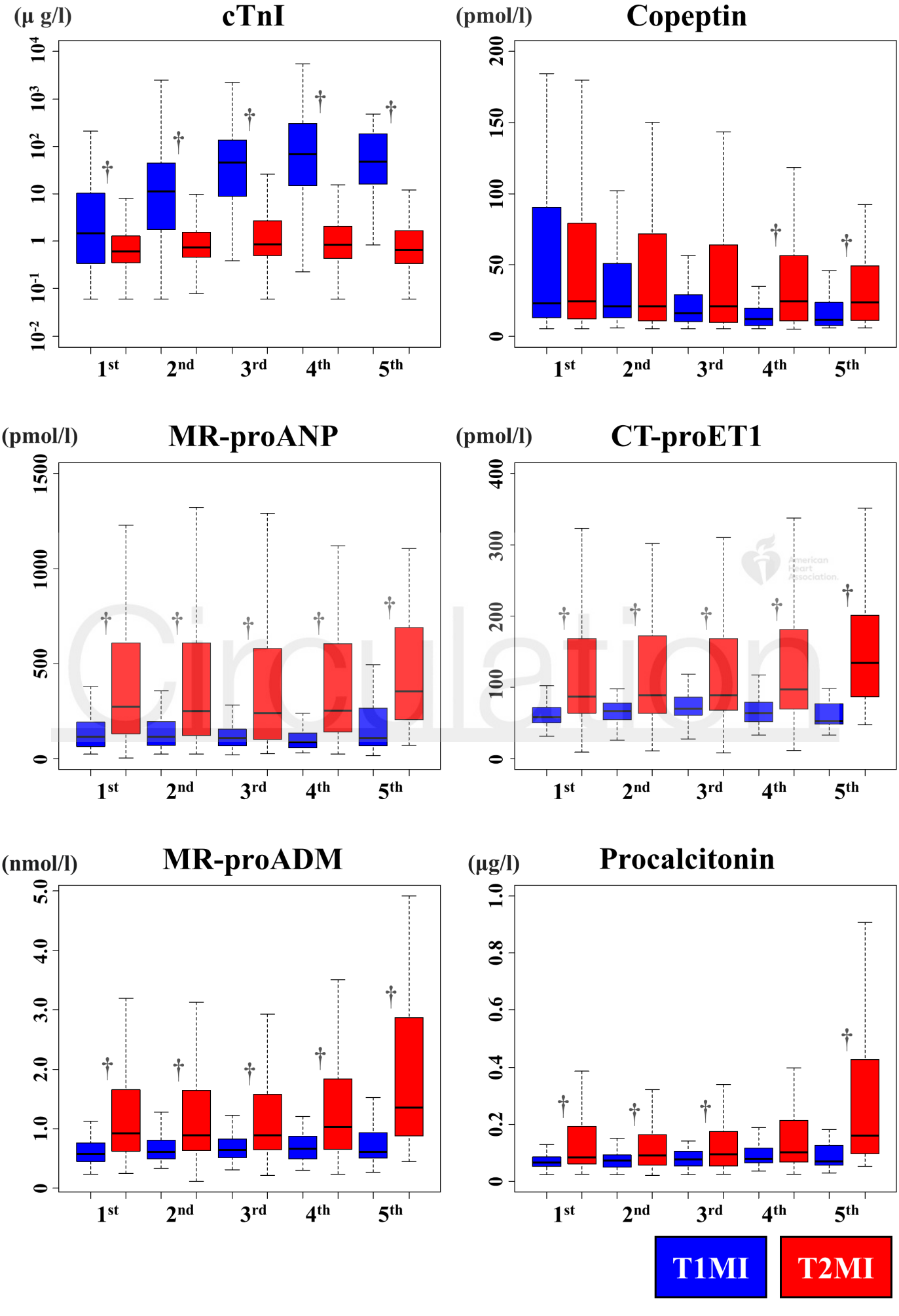


Figure 2A

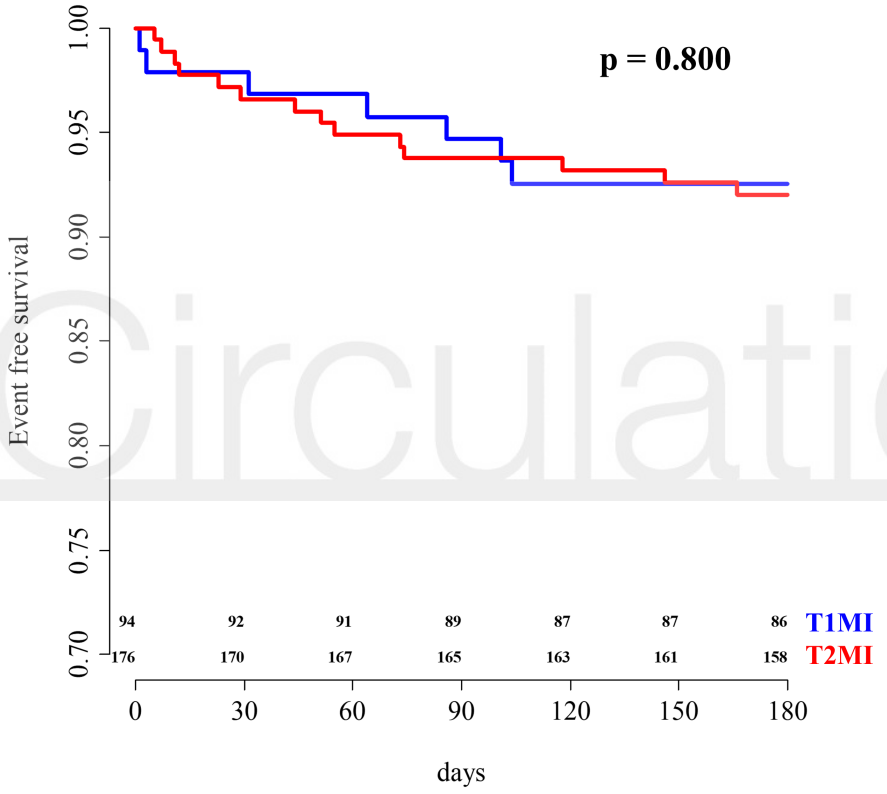
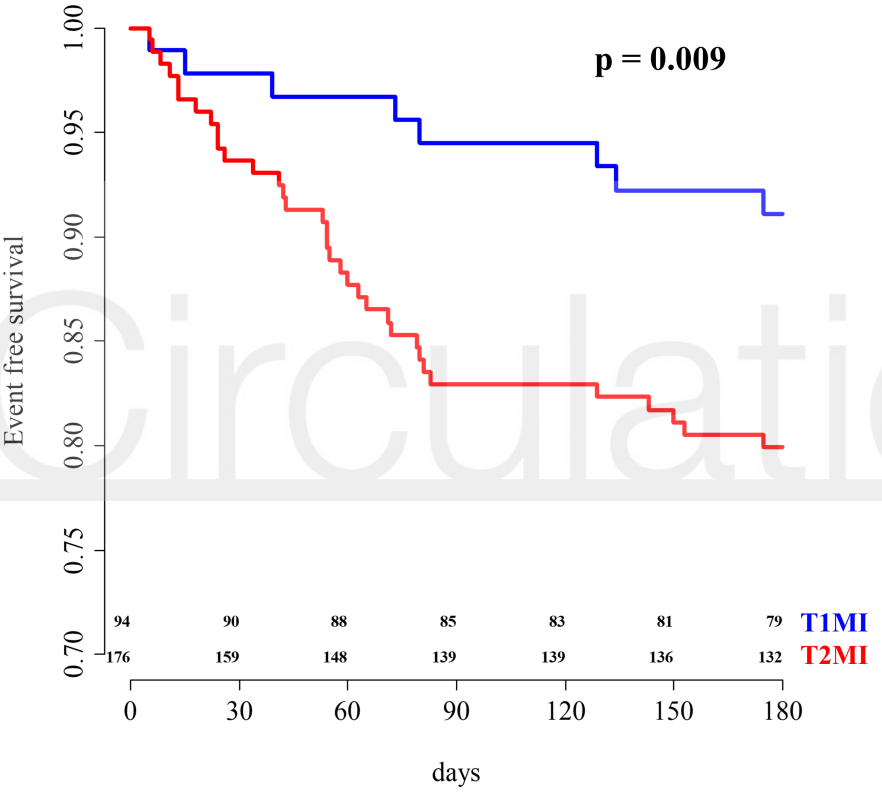
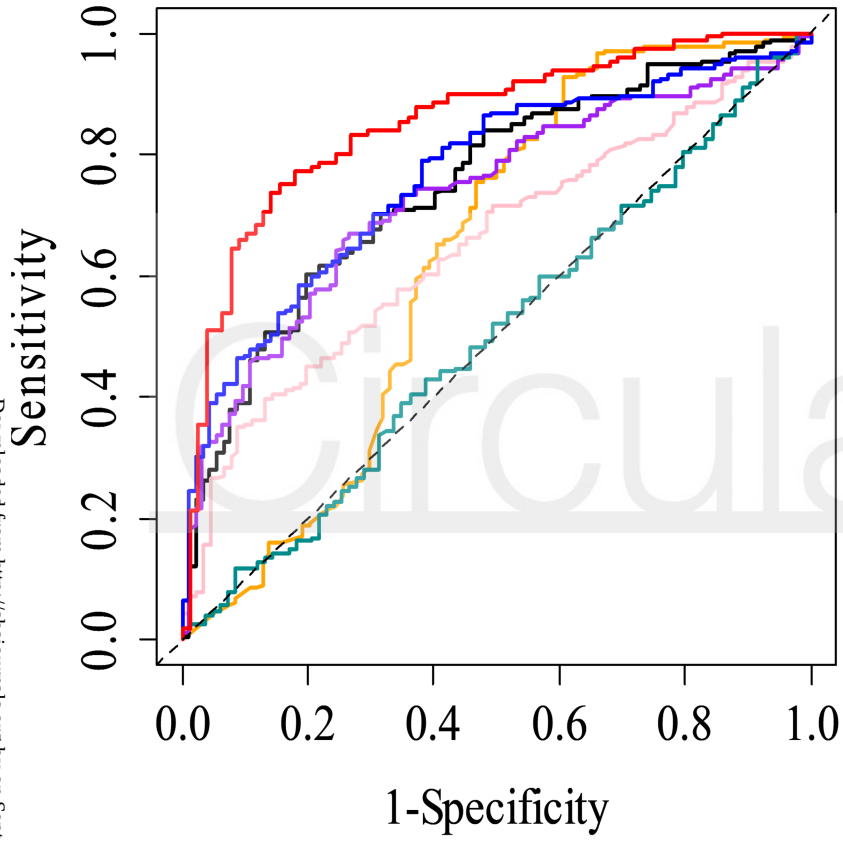


Figure 2B





	AUC	95% CI
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Copeptin	0.501	0.423-0.579
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CT-proET1	0.765	0.707-0.822
MR-proADM	0.750	0.690-0.810
Procalcitonin	0.652	0.584-0.719
All biomarkers	0.854	0.802-0.905

Figure 4A

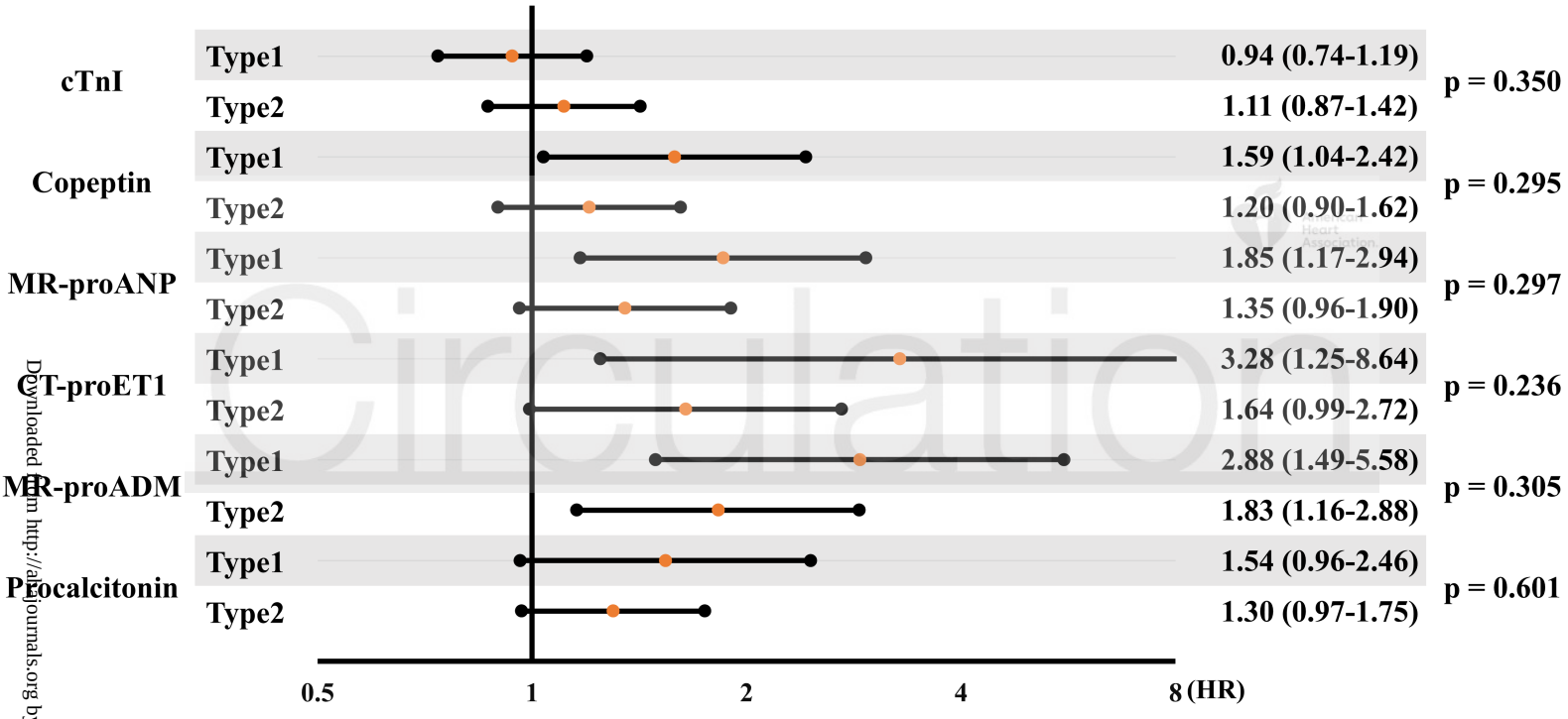

Figure 4B

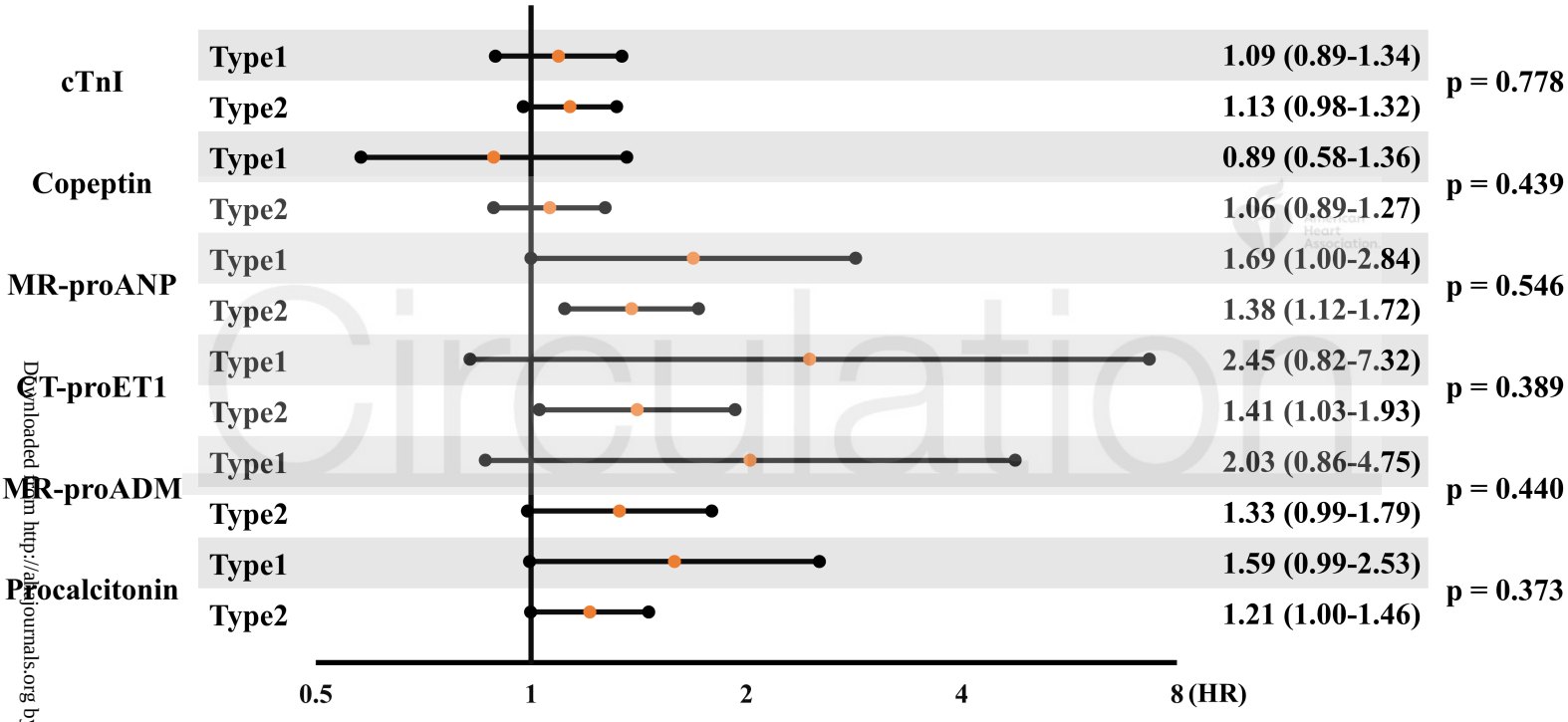

Figure 4C

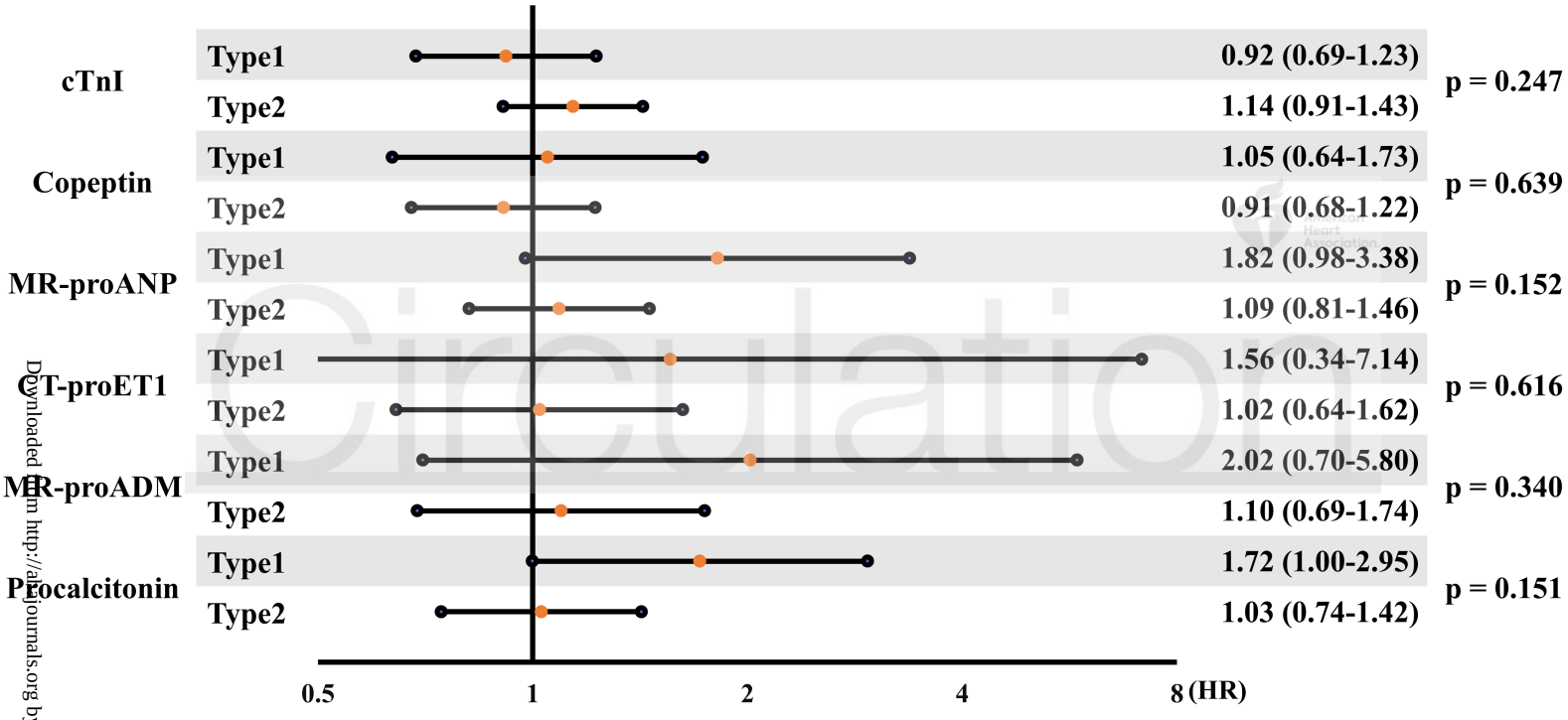

Figure 4D