

Potential Clinical Application of Novel Cardiac Biomarkers for Acute Myocardial Infarction

Alvin Nursalim¹, Marzuki Suryaatmadja², Marulam Panggabean³

¹ Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia. ² Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia. ³ Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence mail:

dr. Alvin Nursalim. Komplek Green Mansion, jalan Green Diamond 3 no: 36, Daan Mogot, Jakarta Barat.
email: Alvin.Nursalim@yahoo.com

ABSTRAK

Penyakit jantung koroner merupakan penyebab utama kematian terkait kardiovaskular. Oleh karena itu, diagnosis sindrom koroner akut yang cepat dan tepat amat diperlukan. Pemeriksaan laboratorium yang merupakan baku emas saat ini seperti troponin dan CK-MB memiliki kekurangan seperti ambang deteksi yang tertunda. Hal ini akan menyebabkan tertundanya diagnosis dan terapi untuk pasien. Oleh karena itu, diperlukan biomarker baru yang meningkat dengan cepat, akurat dan dapat memberikan informasi prognosis.

Terdapat beberapa biomarker jantung baru yang patut diketahui. High sensitivity troponin memiliki kepekaan dan akurasi yang lebih tinggi untuk deteksi dan eksklusi infark miokard akut. BNP dan NT-proBNP memberikan informasi prognostik mortalitas. Myeloperoksidase dapat mengidentifikasi pasien dengan peningkatan risiko kejadian kardiovaskular walaupun tanpa nekrosis miokard. Kombinasi copeptin dan troponin T merupakan pemeriksaan yang lebih akurat untuk mendiagnosis infark miokard akut. Kadar Growth Differentiation Factor-15 berhubungan dengan risiko kematian akibat infark miokard dalam enam bulan ke depan. Sedangkan, pemeriksaan Heart-Fatty Acid Binding Protein dapat mendeteksi lebih awal dan memberikan informasi prognostik serta dapat menggolongkan status risiko pasien. Biomarker baru mengeksklusi infark miokard akut lebih cepat dengan akurasi yang tinggi. Manfaat klinis biomarker baru ini tidak hanya terbatas pada diagnosis infark miokard, seperti biomarker terdahulu. Namun, biomarker jantung baru memiliki potensi tambahan seperti menentukan prognosis pasien dan menggolongkan risiko pasien yang pada akhirnya dapat menentukan langkah terapi selanjutnya yang lebih baik.

Kata kunci: biomarker, infark miokard akut, Hs troponin, B-natriuretic peptide (BNP), myeloperoksidase, copeptin, growth differentiation factor-15 (GDF-15), heart-fatty acid binding protein (H-FABP).

ABSTRACT

Coronary heart disease is the leading cause of cardiac related death worldwide. Therefore, early and accurate diagnosis of acute coronary syndrome is required to determine the next clinical step. The current gold standard for cardiac markers, troponin and CK-MB have their downside. The delayed increase of detectable circulating level of these markers contribute to delayed diagnosis and therapy. Novel biomarkers that rise earlier, has a good diagnosis accuracy and has additional prognostic information, are highly needed.

There are some potential emerging novel biomarkers for acute myocardial infarction. High sensitivity troponin have a greater sensitivity and accuracy for detection and early exclusion of myocardial infarction, as compared to troponin. B-natriuretic peptide (BNP and NT-pro BNP) provide prognostic information in regards of mortality. Myeloperoksidase identify subjects with increased risk of cardiac events in the absence

of myocardial necrosis. Dual marker strategy combining copeptin with troponin T is more accurate assay to diagnose acute myocardial infarction. The level of Growth Differentiation Factor-15 is correlated with the risk of death or myocardial infarction in the next 6 months. While, Heart-Fatty Acid Binding Protein assay is an earlier marker for myocardial necrosis and provide valuable prognostic information and can further stratify patients' risk. Novel cardiac biomarkers provide a faster exclusion of acute myocardial infarction, yet with very good accuracy. However unlike their predecessors, the clinical use of these novel cardiac biomarkers are not only limited to establishing the diagnosis of myocardial infarction. Novel cardiac biomarkers possess additional potential use, some of which are to determine patients' prognosis and to further stratify patients' risk that would determine the next step of therapy.

Key words: biomarkers, acute myocardial infarction, Hs troponin, B-natriuretic peptide (BNP), myeloperoxidase, copeptin, growth differentiation factor-15 (GDF-15), heart-fatty acid binding protein (H-FABP).

INTRODUCTION

The world of science is the world of never-ending quest to progress. The advance in medical science always brings new insight for doctors. At the moment, one medical progress noteworthy to know is the finding of novel cardiac biomarkers for acute myocardial infarction (AMI).

Cardiac biomarkers were first introduced in the 1950s, the investigators reported that certain cardiac protein released from necrotic cardiac myocytes would sign acute myocardial infarction. Many years later, cardiac biomarkers became a routine examination in selected patients, some of which are troponin and CK-MB.¹ As our understanding of the pathophysiology of AMI advances, so does the finding of other potential cardiac biomarkers.

Cardiovascular disease is the leading cause of death in developed countries and it is predicted to be the number one killer in developing countries in the year of 2020. Coronary heart disease is the most common culprit of cardiac related death, therefor AMI with its diverse clinical manifestation should be promptly diagnosed and treated.²

From a clinical point of view, the term commonly used to describe the spectrum of coronary artery disease is acute coronary synrome (ACS). ACS is a life threatening condition, which is usually precipitated by acute thrombosis induced by a ruptured coronary plaque causing a sudden and critical reduction in blood flow. ACS refers to a spectrum of clinical manifestations ranging from ST-segment elevation myocardial infarction (STEMI), non-

ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). There is an elevated level of cardiac biomarker in NSTEMI and STEMI, which reflects myocardial cellular damage. While in UA there is no elevation of cardiac biomarkers.^{3,4}

Ruling out AMI is expensive and time consuming. Sometimes, doctors can not fully rely on clinical findings and ECG examination, since one quarter to one third of patients with AMI present without significant ECG changes. Current guideline recommend the meassurement of cardiac biomarkers (troponin) for differentiation between unstable angina and myocardial infarction (NSTEMI, STEMI).³ However, the current cardiac marker assay i.e. as troponin has its own downside. The delayed rise of troponin after AMI warrant doctors to monitor their patients in the emergency room for a longer period of time (**Figure 1**). Not only this approach cause overcrowding in the emergency department, but also a waste of time and money. Therefore, rapid and reliable way to diagnose AMI is required.⁵ In the absence of typical findings of AMI and without any increase of classic cardiac biomarkers such as troponin and CK-MB, it is helpful to have other biomarkers to assist doctor in making clinical judgement and to determine patients' prognosis.^{5,6}

The aim of this review is to elaborate some novel cardiac biomarkers that possess diagnostic and prognostic value. We will try to answer the intriguing question about novel cardiac biomarkers. Are these biomarkers better than the classic biomarkers in terms of faster

and accurate AMI diagnosis? Biomarkers that would be discussed in this article, include: high sensitivity troponin, B-type natriuretic peptide, N-Terminal pro BNP, myeloperoxidase, growth differentiation factor-15 and heart-type fatty acid-binding protein.

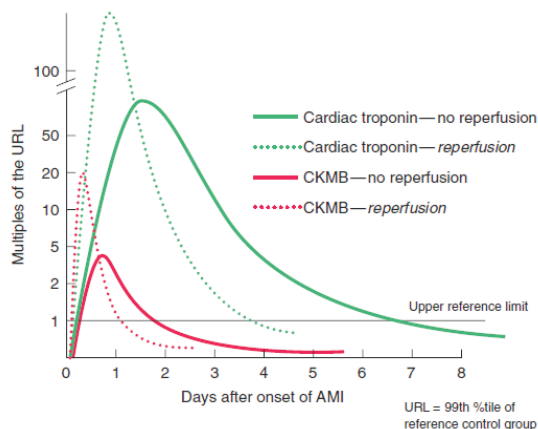


Figure 1. The duration needed for typical cardiac biomarkers to rise in response to infarction. Note the difference between patients who undergo reperfusion and those who do not.⁷

THE RELATIONSHIP BETWEEN NOVEL BIOMARKERS AND THE ATHEROSCLEROTIC PROCESS

The emergence of novel cardiac biomarkers was inseparable from the underlying pathogenesis of atherosclerosis. In getting to know these cardiac biomarkers, one should understand the

multiple factors involved in AMI pathogenesis.

Most cases of myocardial infarction are caused by an occlusion of a coronary artery. Coronary occlusion are usually due to physical disruption of an atherosclerotic plaque with subsequent formation of an occluding thrombus. This occlusion would finally lead to blood flow reduction to the affected myocardium. Atherosclerosis is a chronic disease and involve multiple inflammation components. The process started with the oxidation of LDL cholesterol. Macrophage will then ingest the oxidized cholesterol and form a foam cells. These foam cell become fatty streak that ultimately become the core of atherosclerotic plaque. The migration of smooth muscle cell would strengthen the plaque and the whole process would end with a fibrous capsule with lipid core.^{3,4}

There are multiple underlying factors involved in the progression of AMI. Beside myocyte necrosis, other events such as inflammation, vascular damage and hemodynamic stress also occur. Each of these particular event would yield certain substrate that can be used as cardiac biomarkers.^{1,8,9} Each novel cardiac biomarkers has its own mechanism of production (**Table 1**).

HIGH SENSITIVITY TROPONIN

Troponins consists of three regulatory proteins (troponin C, troponin I and troponin T)

Table 1. Novel biomarkers and the underlying process of production

Novel biomarkers	Mechanism of production	Description
Hs troponin ¹⁰	Released from ischemic cardiomyocyte	Troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin, which results in contraction and relaxation of striated muscle. Hs troponin is the latest generation of troponin assay with better accuracy.
BNP and NT-pro BNP ¹¹	Released from ischemic cardiac ventricle	BNP is a neurohormone synthesized and released from the cardiac ventricles in response to multiple stimulus like ischemic ventricle and increased wall tension
MPO ⁵	Inflammation	MPO is the catalyst for oxidant generation within the artery wall in cardiovascular disease.
Copeptin ⁶	Systemic stress	Copeptin is a C-terminal part of the vasopressin prohormone and secreted in equimolar amounts to vasopressin
GDF-15 ¹²	Released by ischemic cardiomyocyte	GDF-15 is a member of the transforming growth factor-β superfamily that was first identified as macrophage-inhibitory cytokine-1.
H-FABP ¹³	Released by ischemic cardiomyocyte	H-FABP is a low-molecular-weight protein involved in the intracellular uptake and buffering of free fatty acids in the myocardium.

hs troponin: high sensitivity troponin, BNP= B-type natriuretic peptide, NT-pro BNP=N-Terminal pro BNP, MPO= Myeloperoxidase, GDF-15:Growth Differentation Factor-15, H-FABP:Heart-type fatty acid-binding protein.

that control the calcium-mediated interaction of actin and myosin, which results in contraction and relaxation of striated muscle. While troponin C is expressed by both cardiac and skeletal muscle, troponin I and T are unique to cardiac muscle. Therefore, these proteins can be useful biomarkers for cardiac related injury.¹⁰

Troponin I and T have been selected as the gold standard biomarkers for detection of myocardial necrosis. However, one limitation of current troponin assays is the delayed increased for about three to four hours. A newer generation of cardiac troponin assays are now available, high sensitivity (hs) troponin. Since 2011, European Society of Cardiology (ESC) has included the use of hs troponin in their recommendation to assess patients with suspected acute coronary syndrome. Newer troponin assays have limits of detection far below the 99th percentile of a normal reference population. These hs-troponin assays are more sensitive than conventional assays because hs troponin can be measured in concentrations approximately 10-fold lower than the conventional assays.^{3,14-17}

Reichlin et al. have demonstrated the superiority of hs troponin I and T assays for the detection of AMI as compared to a standard

conventional troponin assay. The diagnosis accuracy of these high sensitivity assays were high with area under the curve ranged (AUC) from 0.94-0.96, all were significantly higher than the conventional troponin assay (AUC: 0.90). These assays improve the early diagnosis of AMI.¹⁴ Body et al also documented that with a lower detection limit, hs troponin T has very high sensitivity for AMI at time of presentation. Undetectable hs troponin T has also very high negative predictive value (100.0%, 95% CI: 98.1% to 100.0%) which may be considered for rapid exclusion of AMI.¹⁵ As documented by Omland T et al, hs troponin provide prognostic information among patients with stable coronary artery disease. A detectable value of hs troponin among this population is related with higher risk of heart failure and cardiovascular death.¹⁶

Recent ESC guideline on acute coronary syndrome recommend hs troponin assay for rapid ruling out of myocardial infarction (**Figure 2**). According to this guideline, a rapid rule-out protocol is recommended when highly sensitive troponin tests are available (class Ib recommendation).³ Recent advance in troponin assays provide a greater accuracy for detection and early exclusion of myocardial infarction.

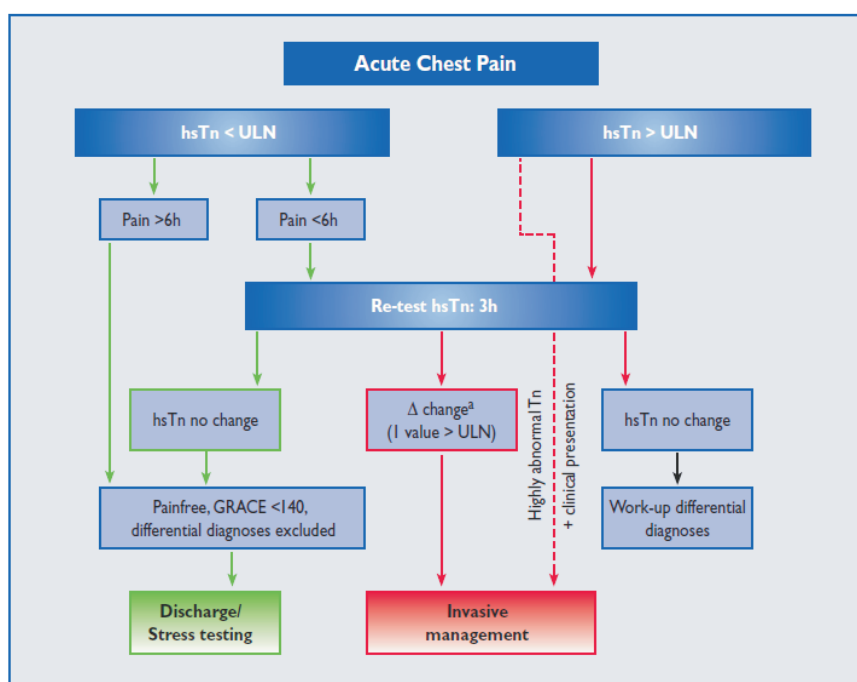


Figure 2. Algorithm recommended by ESC to rapid rule out of acute coronary syndrome with high-sensitivity troponin. GRACE= Global Registry of Acute Coronary Events; hs Tn=high sensitivity troponin; ULN= upper limit of normal.³

BNP AND NT-PRO BNP

B-type natriuretic peptide (BNP) is a cardiac neurohormone that is synthesized and released from cardiac ventricle in response to multiple stimuli including hypoxia, ischemia, exercise, increased wall stress, and dilation of the ventricles. BNP is produced as a prohormone, pro-BNP, which is enzymatically cleaved into BNP and the amino-terminal portion of the prohormone, NT-proBNP.^{11,18} NT-pro BNP levels are known to be associated with ventricular dysfunction.¹⁹ The gene expression of this molecule also increased in response to cardiac hypoxia.²⁰

Recent studies documented the role of BNP and NT-proBNP in adding valuable prognostic information for patients presenting with myocardial infarction. In a study performed by Morrow DA, patients with elevated BNP (>80 pg/ml) were at higher risk of death at seven days (2.5% vs. 0.7%, $P=0.006$) and six months (8.4% vs. 1.8%, $P<0.0001$), independent of troponin I value.¹⁸

In an analysis by Jernberg T, et al. on several trial, NT-pro BNP is strongly related with mortality in patients with suspected or confirmed unstable CAD. In the FAST study, increasing quartile was associated with increased risk of death among patients with suspected of acute coronary syndrome, with a relative risk of subsequent death of 4.2 (1.6–11.1), 10.7 (4.2–26.8) and 26.6 (10.8–65.5), in the 2nd, 3rd and 4th NT-pro BNP quartile, respectively. While in the GUSTO IV trial, increasing quartiles of NT-proBNP were also related to short and long term mortality among non ST elevation patients at 1 year (1.8%, 3.9%, 7.7% and 19.2%, respectively $P<0.001$).²¹ Hence based on these studies, BNP and NT-pro BNP could provide useful prognostic information in regards of mortality in patients with acute coronary syndrome.

MYELOPEROXIDASE

Myeloperoxidase (MPO) is a haemoprotein released during degranulation of neutrophils and monocytes. There is accumulating evidence of polymorphonuclear neutrophils involvement in the process of myocardial injury.^{23,24} MPO plays an important role in atherogenic process

by oxidizing LDL cholesterol, that would eventually become foam cell, the core of atherosclerotic plaque. MPO is also involved in other multiple process throughout the atherosclerosis progression like activation of protease cascades and promotion of endothelial cell apoptosis, leading to breakdown of fibrous cap.^{24,25}

According to Brennan ML et al. MPO levels correlated with troponin T levels and were predictive of AMI ($P<0.001$). Patients in the highest MPO quartile had a 3.9 fold higher chance of having a myocardial infarction on presentation. Whereas troponin T take three to six hours to rise following chest pain, MPO levels already rise even within two hours after the onset of symptoms. MPO measurement is particularly useful when patients presenting with chest pain, yet their troponin T is still negative (<0.1 ng per milliliter).⁵

Another interesting findings from this study is that MPO is a reliable marker for vulnerable plaque. So, MPO can be used as predictor whether or not patients with chest pain but who have no evidence of myocardial necrosis (negative for troponin T) would develop any adverse cardiac events in the future. Among patients who were negative for troponin T, the frequency of adverse cardiac events at 30 days and 6 months increased with increasing base-line MPO quartiles ($P<0.001$ for trend). Subjects in the highest MPO quartile had a higher likelihood of developing adverse cardiac event in the ensuing 30 days and 6 months as much as 4.7 fold.⁵

The prognostic value of MPO was also documented by Baldus S et al. MPO levels predict future risk of subsequent cardiovascular events. Patients with high level of MPO ($>350\mu\text{g/L}$) have a higher risk of developing cardiac event in the ensuing 30 days (adjusted hazard ratio 1.8; $P=0.013$) and 6 months (adjusted hazard ratio 2.1; $P=0.006$).²⁶

COPEPTIN

The level of arginine-vasopressin (AVP) have been shown to be elevated in heart failure and other endogenous stress condition such as critically ill patients.^{27,28} However, AVP is

known to be unstable and rapidly cleared from circulation. Copeptin is a C-terminal part of the vasopressin prohormone and secreted in equimolar amounts to vasopressin. In contrast to AVP, copeptin is stable for days and can be quickly measured.²⁹

Whether copeptin can be a useful marker for rapid diagnosis of AMI had been studied by Reichlin T et al. There are some major findings in this study. First, copeptin levels rise as early as 0-4 hours after onset of symptoms. Copeptin levels were significantly higher in patients with AMI than in patients with other diagnoses ($P < 0.001$). Whereas it is common practise to monitor all patients for ruling out AMI, now a more efficient approach can be implemented. Based on this study, repeated ECG monitoring and serial blood sampling, could be limited to only those patients positive for either troponin T ($> 0.01 \mu\text{g/l}$) or copeptin ($\geq 14 \text{ pmol/l}$). While for those patients whose both markers are negative, monitoring and serial blood sampling are no longer required. Low level of copeptin ($< 14 \text{ pmol/l}$) combined with low level of troponin ($T \leq 0.01 \mu\text{g/l}$) exclude the diagnosis of AMI with high sensitivity (98.8%) and negative predictive value of 99.7%. This dual marker strategy which combine both troponin T and copeptin can be used for a rapid and reliable means for exclusion of AMI. This approach would save the patients from ponderous spending on monitoring and laboratory assay.⁶

Khan AQ et al. documented the prognostic value of elevated copeptin among patients with AMI. In this cohort study, copeptin levels were highest in patients who died or were readmitted to the hospital for heart failure compared with survivors ($P < 0.0005$). Patients with NT-proBNP level above 900 pmol/L and copeptin level above 7 pmol/L were associated with poorer outcome ($P < 0.0005$). In terms of prognostic value for death and heart failure, the combination of copeptin and NT-proBNP assay would yield a larger area under the curve (0.84) than for NT-proBNP alone ($P < 0.013$) or copeptin alone ($P < 0.003$).³⁰

GROWTH-DIFFERENTIATION FACTOR-15

Growth-differentiation factor-15 (GDF-15) is a member of the transforming growth factor- β

superfamily. Recent studies evaluated the levels of GDF-15 among mice whose heart are ischemic. These studies conclude that GDF-15 expression levels rapidly increase in the ischemic area after coronary artery ligation, pressure overload, heart failure and remain elevated in the myocardium after reperfusion for several days.^{31,32}

One study that evaluate the potential use of GDF-15 for human is a study that involve 479 patients with acute chest pain by Eggers KM et al. The value of GDF-15 is divided into three category, normal value ($< 1200 \text{ ng/L}$), moderately elevated ($1200-1800 \text{ ng/L}$) or markedly elevated ($> 1800 \text{ ng/L}$). The more elevated patients' GDF-15 level on admission, the greater risk of composite endpoint (death or myocardial infarction) in the next 6 months. The risk of composite endpoint after six months were 1.3%, 5.1% and 12.6% in patients with normal value, moderately elevated and markedly elevated levels of GDF-15 respectively ($P < 0.001$). GDF-15 is a strong biomarker of adverse outcome in patients with acute chest pain. According to this study, GDF-15 may be valuable for early triage and therapeutic decision-making.³³

Wollert KC et al. also studied the prognostic value of GDF-15 among a more specific group of patients which are patients non-ST elevation acute coronary syndrome (NSTEMI). With the similar grouping of GDF-15 levels as mentioned in the previous study by Eggers KM et al, the higher patients' GDF-15, the higher patients' risk of mortality. The risk of mortality is 1.5%, 5.0% and 14.1% in patients with normal value, moderately elevated and markedly elevated levels of GDF-15 respectively ($P < 0.001$). This study further confirm the potential use of GDF-15 to provide prognostic information for patients with NSTEMI.¹²

HEART-TYPE FATTY ACID-BINDING PROTEIN

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight protein involved in the intracellular uptake and buffering of free fatty acids in the myocardium.¹³ Due to its small size, this molecular is secreted early during myocardial infarction, just when ischemic cardiomyocyte membrane was damaged. Levels

of H-FABP are detectable as early as 1 to 3 hours with peak level at 4 hours and return to baseline level within 24 hours. H-FABP appears to be a very stable protein in vitro for clinical diagnostic purposes. Therefore, H-FABP is a potential marker for early myocardial infarction, even it is believed to be valuable for detecting myocardial ischemia.³⁴

Multiple studies documented the value of H-FABP assay for early myocardial infarction detection.^{35,36} According to McCann CJ et al. the sensitivity of H-FABP assay in the first 4 hours after symptom onset was significantly higher than troponin T (73% versus 55%, $P=0.0043$), however the specificity of H-FABP was rather low 71%. The combination of both these markers increased the sensitivity of H-FABP or troponin T (85%, $P<0.004$).³⁵

H-FABP assay also provide valuable prognostic information beyond what troponin has to offer among patients with acute coronary syndrome.^{13,37} According to Viswanathan K et al there was an increased risk of mortality among patients whose troponin I was negative but H-FABP values are high (threshold level of 6.48 $\mu\text{g/l}$), as compared to those with H-FABP below

the threshold level (hazard ratio: 11.20, 95% CI: 4.95-25.36, $P<0.001$). Those patients whose H-FABP level exceed threshold level are deemed to be closely monitored and further examined by more advanced examination like coronary angiography.¹³

THE FUTURE PROSPECT OF NOVEL BIOMARKERS

To date, cardiac troponin remains the most widely used assay in myocardial infarction diagnosis. Beside the delayed increased, conventional troponin lacks the ability to detect early phase ischemia in the absence of necrosis. Therefore patients who are at increased risk of cardiac adverse outcome remains undetected.³⁸ Novel biomarkers provide additional information in addition to those already provided by troponin assay, which include early detection of myocardial ischemia, sign of unstable plaque and determine patients' prognosis. Studies regarding novel biomarkers are summarized in **Online Table** (www.inaactamedica.org/archives/2013/appendix/nursalim_vol.45-p.240.pdf). While **Table 2** provide information in regards of potential future use of novel cardiac biomarkers.

Table 2. The potential use of novel biomarkers

Novel biomarkers	Potential use		Description
	Diagnostic	Prognostic	
Hs Troponin ^{15,16,17}	√	√	<ul style="list-style-type: none"> - This assay has a greater accuracy for detection and early exclusion of myocardial infarction. - Increased hs troponin level predicts future heart failure and cardiac related mortality.
BNP and NT-pro BNP ^{18,21}		√	<ul style="list-style-type: none"> - BNP and NT-pro BNP provide prognostic information in regards of mortality. The higher the value of these markers the higher risk of mortality.
MPO ^{5,26}	√	√	<ul style="list-style-type: none"> - MPO identified subjects with increased risk of cardiac events in the absence of myocardial necrosis. - MPO is a sign of vulnerable plaque and could be a reliable predictor of future cardiac events.
Copeptin ^{6,30}	√	√	<ul style="list-style-type: none"> - Dual marker strategy combining copeptin with troponin T is a more accurate assay to diagnose AMI. - This dual marker approach is also a rapid and reliable way to exclude AMI
GDF-15 ^{12,33}		√	<ul style="list-style-type: none"> - GDF-15 is a strong biomarker of adverse outcome in patients with acute chest pain. - GDF-15 may be valuable for early triage and therapeutic decision-making
H-FABP ^{13,35}	√	√	<ul style="list-style-type: none"> - H-FABP is a potential marker for early myocardial infarction, it can even be used for detecting myocardial ischemia. - H-FABP assay also provide valuable prognostic information and can further stratify patients' risk.

There is a trend towards multimarker approach which combine both classic and novel markers to stratify patients' risk, to guide doctors in clinical decision-making and to determine patients' prognosis (troponin T and copeptin; troponin T and NT-proBNP; NT-proBNP and copeptin). This multimarker approach is a promising measure to detect AMI during the early phase and stratify patients' risk.^{6,18,28} **Figure 3** and **Figure 4** provide a proposed algorithm for guiding clinical management on patients with suspected myocardial infarction using troponin combined with either copeptin or H-FABP. Please be noted that these algorithms are the translation from existing studies and required further validation to be implemented in daily clinical practise.^{6,13}

We are just entering the new era of novel biomarkers assay and most of these biomarkers might not widely available for routine clinical use at the moment. From the above mentioned novel cardiac biomarkers, biomarkers have been suggested for clinical use in the guideline by European Society of Cardiology is hs troponin and BNP/NT-pro BNP, while others still require

further assessment.³ There are some questions to be addressed in future research. Firstly, which biomarker or combination of biomarkers from all those already available, are best in making diagnoses of AMI in terms of sensitivity and specificity? Secondly, is there any particular patients' characteristics that would benefit most by these extra assays? If there was such data, then this assay can be targeted to a more specific group of patients, especially at current times where guideline are not available. This question is also related to the patients' burden upon this assay. If this assay is about to be applied widely then cost-effectiveness is another crucial aspect to be considered, which lead to the third question regarding the cost effectiveness of these biomarkers for cardiovascular routine screening. Then the cut off value of this novel biomarkers also need to be standardized. Whether ethnic group, age, or other factors contribute to the cut off value also need to be further investigated.

To date, there is no cardiac biomarkers that can reliably describe the early phase of cardiovascular disease continuum or to mark the early progression of atherosclerotic plaque. The

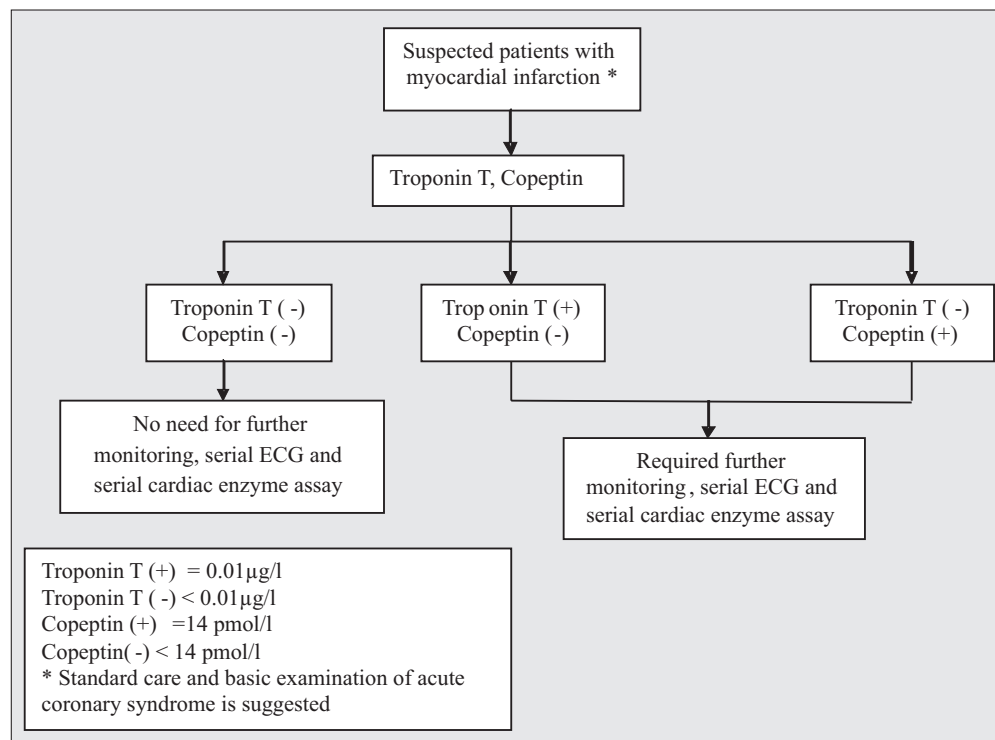


Figure 3. A proposed algorithm for diagnosis, early exclusion and evaluation of AMI based on copeptin and troponin T⁶

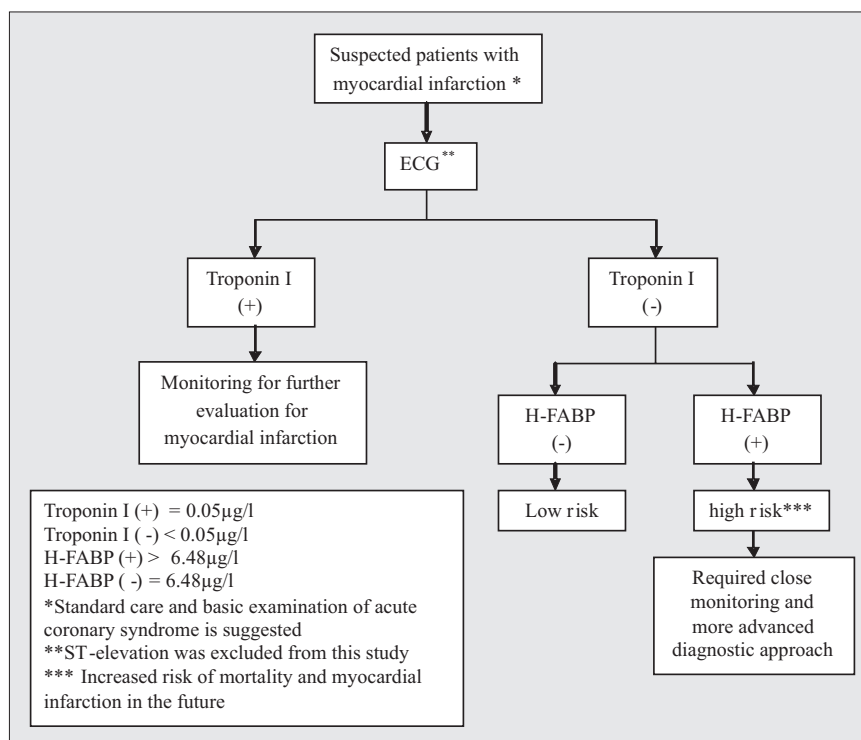


Figure 4. A proposed algorithm for prognosis and risk stratification of AMI based on H-FABP and troponin I¹³

lack of early biomarkers are today's unmet need, that would be otherwise be a potential marker for disease prevention and warrant doctors for a more aggressive disease intervention and monitoring.³⁹

These biomarkers are not widely applied at the moment and there might be new information about this biomarkers yet to be discovered. Future research hopefully would provide further insight in regards of patient's characteristic that would benefit most from this biomarkers analysis, the cost-effectiveness of these assays and the cut-off value for each biomarker. Finally, a globally agreed consensus on this matter would provide guideline for doctors to perform a cost-effective laboratory examination on the right patients.

CONCLUSION

Novel cardiac biomarkers, when used individually or in combination, provide a faster exclusion of AMI, yet with very good accuracy. In addition to save time and money, rapid exclusion of AMI would lead to a better management of patients with AMI that would hopefully lead to reduction of AMI related mortality and morbidity

The clinical use of cardiac biomarkers are not only limited to establishing the diagnosis of myocardial infarction like they used to be. Novel cardiac biomarkers possess huge potential, one of which is to further stratify patients' risk and prognosis that would finally determine the next step of therapy.

REFERENCES

- Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes, moving toward a multimarker strategy. *Circulation*. 2003;108:250-2.
- Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. doi:10.1093/eurheartj/ehr236. Diunduh dari: <http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/ACS-non-ST-segment-elevation.aspx>.
- Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2011;32:2999-3054.
- Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis from pathophysiology to practise. *J Am Coll Cardiol*. 2009;52:2129-38.

5. Brennan ML, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med.* 2003;349:1595-604.
6. Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol.* 2009;54:60-8.
7. Antman EM, Braunwald E. ST-segment elevation myocardial infarction. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principle of internal medicine.* 16th edition. New York: McGraw Hill; 2005. p. 1448-59.
8. Libby P. Current concept of the pathogenesis of the acute coronary syndrome. *Circulation.* 2001;104:365-72.
9. Braunwald E. Unstable angina, an etiologic approach to management. *Circulation.* 1998;98:2219-22.
10. Reiter M, Reichlin T, Twerenbold R, Mueller C. Diagnosis of acute myocardial infarction using highly sensitive cardiac troponin assays. *Euro cardiol.* 2011; 7:18-30.
11. Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. *Am Heart J.* 1998;135:914-23.
12. Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST elevation acute coronary syndrome. *Circulation.* 2007;115:962-71.
13. Viswanathan K, Kilcullen N, Morrell C, et al. Heart-type fatty acid-binding protein predicts long term mortality and reinfarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. *J Am Coll Cardiol.* 2010;55:2590-8.
14. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361:858-67.
15. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol.* 2011;58:1332-9.
16. Omland T, De Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med.* 2009;361:2538-47.
17. Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. *Vasc Health Risk Manag.* 2010;6:691-9.
18. Morrow DA, De Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/Non-ST elevation myocardial infarction. *J Am Cardiol.* 2003;41:1264-72.
19. Santosa Y, Tjandrawati A, Noormartany, et al. Comparison of Pro B-Natriuretic Peptide in hypertensive patients with and without diastolic dysfunction. *Acta Med Indones.* 2008;40:19-23.
20. Ferdinal F, Suyana FD, Wanandi SI, Sadikin M. Expression of B-type Natriuretic Peptide-45 gene in the ventricular myocardial induced by systemic chronic hypoxia. *Acta Med Indones.* 2009;41:136-43.
21. Jernberg T, James S, Lindah B, Stridsberg M, Venge P, Wallentin L. NT-pro BNP in unstable coronary artery disease-experiences from the FAST, GUSTO IV and FRISC II trials. *Eur J Heart Failure.* 2004;6:319-25.
22. Zhang R, Brennan ML, Shen Z, MacPherson JC, Schmitt D, Molenda CE, Hazen SL. Myeloperoxidase functions as a major enzymatic catalyst for initiation of lipid peroxidation at sites of inflammation. *J Biol Chem.* 2002;277:46116-22.
23. Morrow DA, Sabatine MS, Brennan ML, De Lemos JA, Murphy SA, Ruff C. Concurrent evaluation of novel cardiac biomarkers in acute coronary syndrome: myeloperoxidase and soluble CD40 ligand and the risk of recurrent ischaemic events in TACTICS-TIMI 18. *Eur Heart J.* 2008;29:1096-102.
24. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. *Arterioscler Thromb Vasc Biol.* 2005;25.
25. Podrez EA, Febbraio M, Sheibani N, et al. Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species. *J Clin Invest.* 2000;105:1095-108.
26. Baldus S, Heeschen C, Meinertz T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation.* 2003;108:1440-5.
27. Finley IV JJ, Konstam MA, Udelson JE. Arginine vasopressin antagonist for the treatment of heart failure and hyponatremia. *Circulation.* 2008;118:410-21.
28. Jochberger S, Morgenthaler NG, Mayr VD, Luckner G, Wenzel V, Ulmer H, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. *J Clin Endocrinol Metab.* 2006;91:4381-6.
29. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem.* 2006;52:112-9.
30. Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal pro-vasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) Study. *Circulation.* 2007;115:2103-10.
31. Kempf T, Eden M, Strelau J, et al. The transforming growth factor- β superfamily member growth-differentiation factor-15 protects the heart from oschemia/reperfusion injury. *Circ Res.* 2006;98:351-60.
32. Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. *Circ res.* 2006;98:342-50.
33. Eggers KM, Kempf T, Allhoff T, Lindahl B, Wallentin L, Wollert KC. Growth-differentiation factor-15 for early risk stratification in patients with acute chest pain. *Eur Heart J.* 2008;29:2327-35.

34. Viswanathan K, Hall AS, Barth JH. An evidenced-based approach to the assessment of heart-type fatty acid binding protein in acute coronary syndrome. *Clin Biochem.* 2012;33:3-11.
35. McCann CJ, Glover BM, Menown IBA, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. *Eur Heart J.* 2008;29:2843-50.
36. Seino Y, Ogata K, Takano T, et al. Use of a whole blood rapid panel test for heart-type fatty acid-binding protein in patients with acute chest pain: Comparison with rapid troponin T and myoglobin tests. *Am J Med.* 2003;115:185-90.
37. Ishi J, Ozaki Y, Lu J, et al. Prognostic value of serum concentration of heart-type fatty acid-binding protein relative to cardiac troponin T on admission in the early hours of acute coronary syndrome. *Clin Chem.* 2005;51:1397-404.
38. O'Rourke MF, Safar ME, Dzau V. The Cardiovascular Continuum extended: aging effects on the aorta and microvasculature. *Vasc Med.* 2010;15:461-8.
39. Vassiliadis E, Barascuk N, Didangelos A, Karsdal MA. Novel cardiac-specific biomarkers and the cardiovascular continuum. *Biomarker Insight.* 2012;7:45-57.