Review Article

Biomarker Use for Cardiovascular Disorders in the Emergency Department

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ABSTRACT

Background: Cardiovascular disease is the leading cause of mortality worldwide. Emergency department physicians make time-sensitive decisions of urgent treatment and hospitalization versus discharging patients with cardiovascular symptoms. This article will review the role of cardiovascular biomarkers in the emergency room. We will discuss standard biomarkers like troponins/high-sensitivity troponins, CK-MB, myoglobin and natriuretic peptides used in current emergency departments, as well as newer biomarkers that are showing strong data for possible use in the future. (J Clin Prev Cardiol. 2014;3(1):12-20)

Keywords: Cardiovascular biomarkers; emergency department; cardiovascular disease.

Cardiovascular disease (CVD) is the leading cause of mortality worldwide (1). Annually, about 6 million patients present to the emergency department (ED) with chest pain (2). ED physicians have to make the urgent decision of appropriate treatment and hospitalization, or discharging these patients. The ED workup begins with a thorough history and physical finding, electrocardiogram and labs. These labs include biomarkers that have become standard in CVD workup.

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" (3). Further, "an ideal biomarker should be readily available, well tested, have established reference values compared to gold standard, have known sensitivity and specificity, a rapid turnaround time and not be costly" (4).

Table 1 is a list of available cardiovascular biomarkers. This article will review the role of cardiovascular biomarkers in the emergency room. We will discuss standard biomarkers like troponins/high-sensitivity troponins (hsTn), CK-MB, myoglobin and natriuretic peptides (NP) used in current emergency departments, as well as newer biomarkers that are showing strong data for possible use in the future.

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Table 1.

List of various cardiac biomarkers classified in categories of processes they are involved in the development of cardiovascular diseases

Myocardial Necrosis	Troponins/high-sensitivity troponins Creatinine kinase-MB (CK-MB) Myoglobin
Myocardial Strain/Stretch	Brain natriuretic peptide (BNP)/N-terminal pro brain natriuretic peptide (NT-proBNP)
Neurohormones	Norepinephrine Renin angiotensin aldosterone system (RAAS) Endothelin-1 Copeptin
Myocardial Ischemia	Ischemic modified albumin Heart type fatty acid binding protein Choline Tissue factor
Inflammatory	C reactive protein Myeloperoxidase Interleukin (IL) 6 Fas (Apo 1) Tumor necrosis factor alpha (TNF-α) Pentraxin-3 Procalcitonin
Markers of Blood Vulnerability	D-dimer Fibrinogen Prothrombin fragments Plasminogen activator 1
Thrombosis	Von Willebrand factor Soluble CD40 ligand Vascular cell adhesion (VCAM) P-selectin Platelet microparticles Endothelin growth factor, placental growth factor, hepatocyte growth factor
Matrix &Cellular Remodeling	Galectin-3 sST2 Matrix metalloproteinase, matrix metalloproteinase tissue inhibitors. Growth differentiation factor 15 (GDF-15)
Cardiorenal	Cystatin C Neutrophil gelatinase-associated lipocalin (NGAL) B-trace protein

Myocardial Necrosis

Troponins

Troponins are biomarkers that are involved in the contraction of striated muscles and have become the gold standard in detection of myocardial injury. Troponin I and troponin T (cTnT and cTnI, respectively) are specifically found in cardiomyocytes (1). In the setting of cardiomyocyte damage, levels of cTnT and cTnI can increase in the serum within 3–4 hours and remain elevated up to 10–14 days (5). There have been multiple generations of assays for both troponin T and I. One issue with cTnI is the various assays commercially available, with different sensitivity ranges, which has made it difficult to compare between assays (6). cTnT on the other hand has only one commercially available assay making it easier for clinical use and comparison (6). Both these assays have gone through several generations of improvements with the most recent being hsTn. HsTn assays use recombinant monoclonal human antibodies, and have higher precision and lower limit of detection than prior assays (6). The limit of detection for hsTnT is 0.003 ng/mL, the 99th percentile cutoff point is 0.014 ng/mL, and the 10% coefficient of variation is at 0.013 ng/mL (5).

Multiple studies have shown that hsTn assay has stronger diagnostic value than prior generations of TnI and TnT (7,8). The utility of troponins is in its capability to "rule out" MI due to their high sensitivity (7,8). Aldous *et al*. showed that the sensitivity of hsTnT by 2 hours in patients with chest pain was 95.1% for acute myocardial infarction (AMI), while the specificity was 75.6%, the positive predictive value (PPV) was 53.8% and the negative predictive value (NPV) was 98.3% (7). The ≥20% change criteria of hsTnT over the 2 hour period, for 0–2 hour samples, increased specificity to 92.4% while sensitivity dropped to 56.1% (7). Keller *et al*. demonstrated that the use of hsTnI at admission for early detection of AMI (diagnostic cutoff value at the 99th percentile of 30 pg/mL) had a sensitivity of 82.3%, a PPV of 75.1% and an NPV of 94.7%. Addition of 3 hour hsTnI in the same study increased the sensitivity to 98.2%, the PPV to 95.8% and the NPV to 99.4% for AMI (8).

The utility of troponins goes beyond its diagnostic implications. Troponins are strong prognostic biomarkers in patients with myocardial necrosis. Eggers *et al*.'s study showed that in non-ST-elevated MI (NSTEMI) patients, increase of >0.01 µg/L of cTnI (Access AccuTnI assay) predicted mortality during long-term follow-up (5 years) (9). Ohman *et al*. found that in patients with MI (whether electrocardiogram showed ST-segment elevation [STEMI], ST-segment depression, T-wave inversion, bundle-branch block or paced rhythms) mortality within 30 days was 11.8% with higher levels of cTnT versus 3.9% in those with lower levels of cTnT (10). They also showed that cTnT was most strongly correlated to 30-day mortality, followed by electrocardiogram categories, and CK-MB values (10).

The strong implication of elevated cardiac troponins in the emergency room is dampened by the fact that it does not specify the cause of myocardial necrosis. It is important to get a close history and physical finding and combine these findings with electrocardiogram findings and other lab-specific criteria to diagnose MI. There are multiple causes of elevated cardiac troponins and these include tachyarrhythmia, cardiac/chest trauma, heart failure, left ventricular hypertrophy, myocarditis, pericarditis, endocarditis, as well as non-cardiac causes like sepsis, burns, respiratory failure, neurological diseases, pulmonary emboli (PE), drug toxicity, chemotherapy, renal disease/insufficiency, etc. (6. The role of troponins in such disease process may have prognostic value as well, but it is essential to assess elevations of troponin values in the context of patient presentation to direct management.

It is important to mention that troponins in the presence of renal failure are often elevated and, in the ED, it becomes difficult to assess their value, especially only slightly elevated. Studies have shown that in patients with renal disease, cTnT is more often elevated (15–53%) than cTnI (less than 10%), even when no clinical evidence of myocardial necrosis is present (11). However, it is imperative not to ignore troponin elevations in these patients since they are highly prognostic for adverse outcome (12). The exact mechanism causing the elevation of troponins in renal failure is not well understood but experts agree that it may be related to ongoing cardiac disease, renal metabolites and differential clearance (12).

CK-MB

Creatinine kinase – MB (CK-MB) is a cytosolic carrier protein for high-energy phosphate and used as a biomarker for the diagnosis of myocardial necrosis (6). CK-MB is an older marker than troponins and currently used in conjunction with troponins in multimarker cardiac panels in the ED. It is less sensitive and specific for MI than troponins, is present in low levels in healthy individuals, and can increase in patients with skeletal muscle damage due to its presence in different tissues (6). It elevates within ~ 4–6 hours of MI and normalizes

within 2–3 days after the event (6).

Puleo *et al*., in 1990, showed that the presence of elevated isoforms of CK-MB at 2–4 hours after initiation of symptoms had a 59% sensitive for the diagnosis of MI, but after 4–6 hours the sensitivity rose to 92% (13). In addition, some emergency departments use the CK-MB/total creatinine kinase (CK) ratio to evaluate patients with ischemic symptoms since it is highly specific for AMI when >5% (14). The concept of serial biomarker measurement is recommended with the use of CK-MB just as it is with troponins. Young *et al*. showed that 0–3 hour delta CK-MB showed sensitivity of 93% and specificity of 94% for AMI (15). The study also showed that CK-MB had a PPV of 52% at 0 hour and 96% at 3 hour, and NPV of 55% at 0 hour and 99% at 3 hour for AMI (15).

The major utility of CK-MB is in its short half-life and therefore serial measurements allow for detection of early infarction extension, re-infarction and periprocedural MI (6). In the realm of current practice, CK-MB is routinely used along with troponins, but is second choice to troponins in the diagnosis of MI (6).

Myoglobin

Myoglobin is a nonspecific biomarker that is used in combination of other biomarkers in suspected AMI patients in the ED. Myoglobin is an early marker of myocardial injury and can rise within 1–3 hours of the event and rapidly normalizes as well (6). Since myoglobin in not cardiac specific, it is used in conjunction with cardiac-specific biomarkers.

Point of Care Combination Panels

The ACCF/AHA guidelines suggest monitoring troponins along with CK-MB and myoglobin, in serial panels, in ED patients with suspected MI. The late rising biomarkers are more cardiac specific and confirm findings of the more nonspecific early marker (6).

The following are the current ACCF/AHA guidelines regarding cardiac biomarkers in the initial evaluation of patients with suspected AMI.

"Class I #2: Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g., death or re-MI) that focuses on history, including angina symptoms, physical findings, ECG findings, and biomarkers of cardiac injury, and results should be considered in patient management. (Level of Evidence: C)

Class I #5: Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS. (Level of Evidence: B)

Class I #6: A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS. (Level of Evidence: B)

Class I #7: Patients with negative cardiac biomarkers within 6 hours of the onset of symptoms consistent with ACS should have biomarkers re-measured in the time frame of 8 to 12 hours after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.) (Level of Evidence: B)

Class IIb #1: For patients who present within 6 hour of the onset of symptoms consistent with ACS, assessment of an early marker of cardiac injury (e.g., myoglobin) in conjunction with a late marker (e.g., troponin) may be considered. (Level of Evidence: B)

Class IIb #2: For patients who present within 6 hours of symptoms suggestive of ACS, a 2-hour delta CK-MB mass in conjunction with 2-hour delta troponin may be considered. (Level of Evidence: B)

Class IIb #3: For patients who present within 6 hour of symptoms suggestive of ACS, myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min may be considered. (Level of Evidence: B)

Class IIb #4: Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. (Level of Evidence: B)

Class III: Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS. (Level of Evidence: C)" (6).

Studies have shown that faster "rule outs" for MI is possible in the ED. In fact, McCord *et al*. found that 90 minute point of care combination of myoglobin and

troponin I was 96.9% sensitive for AMI and had a 99.6% NPV for AMI (16). CK-MB did not add diagnostic value in this study. Ng *et al*. demonstrated that 90 minute point of care combination of troponin I, myoglobin, and CK-MB had a100% sensitivity, 94% specificity, 47%PPV, and 100% NPV for diagnosis of AMI in patients presenting with chest pain. Their study showed that monitoring for high-risk history, ECG changes, and rapid point of care testing of the 3 markers reduced CCU admission by 40% (17). Last, Biener *et al*. showed that serial cTnT in "ruling-in" and "ruling-out" of NSTEMI can be comparably effective at 3 hours versus 6 hours (18). Of note, for ruling-in NSTEMI, absolute changes performed better than relative concentration changes in all points in the last study (18).

Studies have shown that changes in the baseline threshold value of troponins and baseline absolute value changes in a particular population will reflect on the sensitivity, specificity, PPV and NPV accordingly (19). Such studies should be validated in prospective studies and clinicians should bear in mind their patient population, prevalence of MI in their community, confounding factors, as well as cost-effectiveness and the best use of these tests in their community or practice.

Neurohormones

Myocardial stretch/strain: B type natriuretic peptide (BNP)

B type natriuretic peptide (BNP) is a cardiac neurohormone released primarily from the ventricles in the response to volume expansion and pressure overload (20). BNP reduces both preload and afterload via its natriuretic, diuretic and vasodilatory actions (20).

BNP has become the standard in evaluating patients with dyspnea in the ED to differentiate between cardiac versus noncardiac etiology. Maisel *et al*. in 2002 found that BNP was more accurate than any history or physical findings as well as NHANES and Framingham criteria for diagnosing heart failure (21). The study showed that a cutoff of 100 pg/mL had a sensitivity of 90%, a specificity of 76%, and an accuracy of 83% for differentiating congestive heart failure (CHF) from other causes of dyspnea (21). BNP at 50 pg/mL had a 96% NPV for heart failure versus other causes of dyspnea (21).

Like BNP, NT-proBNP is the precursor of BNP and cleavage product of pro-BNP. Januzzi *et al*. in the PRIDE study found that NT-proBNP was highly sensitive and specific for acute heart failure at levels >450 pg/mL in patients <50 years and >900 pg/mL in patients ≥ 50 years (22). They also found that levels <300 pg/mL had an NPV of 99% for ruling out CHF (22). NT-proBNP was superior to clinical judgment in the diagnosis of heart failure, and NT-proBNP in combination with clinical judgment was superior to either alone for the diagnosis of heart failure (22).

Not only is BNP and NT-proBNP diagnostic in patients with dyspnea, they are likewise prognostic and therefore very useful clinically. BNP allows clinicians to make the decision to admit or discharge patients from the emergency room. Maisel *et al*. showed in the REDHOT study that patients with shortness of breath in the ED with BNP levels <200 pg/mL had a 90-day event rate (including CHF visits, hospitalizations, mortality) of 9% versus those with BNP >200 pg/mL had an event rate of 29% (23). Similarly, NT-proBNP is prognostic of mortality in acute and chronic heart failure (24).

The diagnostic capability of BNP for coronary artery disease and MI is not as accurate as it is for troponins. BNP can rise within the first 24 hours of MI and then stabilize (25). The utility of BNP in MI is in its prognostic value. De Lemos *et al*. showed BNP correlated with mortality, heart failure and myocardial re-infarctions at 10 months in patients with ST-elevated MI (STEMI), NSTEMI and unstable angina. They demonstrated that patients with BNP levels in the increasing quartiles had significantly increased odds ratio for death at 10 months (2nd quartile had odd ratio 3.8, 3rd quartile had odds ratio 4.0, and 4th quartile had odds ratio of 5.8) (26). Likewise, NT-proBNP has also shown strong prognostic correlation in patients with unstable coronary artery disease (6).

As a result, the utility of BNP and NT-proBNP in the ED is twofold. One, they are highly diagnostic in dyspneic patients for heart failure. Two, they are highly prognostic in patients with cardiac ischemic symptoms.

There are special circumstances when clinicians should be careful when interpreting NP levels. NPs are lower in obese patients both with and without heart failure (27). NP values are influenced by renal disease and in low GFR experts have suggested that NP cutoffs may need to be raised (27). Lastly, there exists a "gray zone" level for NP s where there is not much support that CHF is likely or unlikely. The gray zone for BNP is when levels are >100 pg/mL or levels <400 pg/mL. In this BNP range, other causes of myocardial stress than CHF need to be suspected. These causes include pulmonary hypertension, chronic obstructive pulmonary disease, etc. (27).

Copeptin

Copeptin, or c-terminal pro-vasopressin, is synthesized with vasopressin as a precursor, secreted from the hypothalamus, and stored in the pituitary (28). Vasopressin plays a major role in cardiovascular hemodynamic balance by influencing free water absorption, blood volume, body fluid osmolality and vascular tone (28). Vasopressin also plays a role in endocrine stress response (29). Vasopressin, however, has a very short half-life, binds platelets and as a result not an ideal biomarker. Copeptin, on the other hand, is stable and measurable within an hour in current immunoassays (28). It has become a surrogate to measure vasopressin levels.

Reichlin *et al*. showed that patients in the ED with symptoms suggestive of MI had significantly higher copeptin level at presentation than those without MI. In fact, they showed that copeptin level <14 pmol/L along with troponin T ≤0.01 µg/L in combination had a sensitivity of 98.8% and NPV of 99.7% for AMI (30). Copeptin seems to be an early cardiac biomarker that may help reduce the time needed to "rule-out" MI patients in the ED.

Studies have also shown that the role of copeptin is prognostic in patients with heart failure independent of NP (31,32). Data shows that when copeptin is measured in combination with NP, they seem to correlate with higher adverse events (31,32). The prognostic value of copeptin was also seen in post-MI patients in whom it predicted adverse outcome, especially in those with higher NP levels (33).

Copeptin may be used in the ED but it is not specific for the heart. It is elevated in a wide array of disease including respiratory illness, stroke, etc. The ideal cutoff for copeptin use in the ED also needs to be evaluated and further studied. In addition, copeptin level is affected by renal disease as well as with corticosteroid use, which needs to be kept in mind when using this biomarker in the clinical setting (29).

Biomarkers of Ischemic Injury

Oxidative biomarker: Ischemic modified albumin (IMA)

During myocardial ischemia, changes occur at the amino terminal of albumin, which result in changes in its ability to attach to certain heavy metals, specifically cobalt (34). The albumin cobalt binding test measures ischemic modified albumin (IMA), which is an emerging oxidative biomarker.

Current biomarkers used in the ED for cardiac ischemic symptoms are biomarkers that diagnose cardiac necrosis, but they cannot identify those patients with ischemic disease, including patients with stable and unstable angina. IMA is able to identify early those patients with myocardial ischemia who have not yet had myocardial necrosis (34). Anwaruddin *et al*. demonstrated that at 90 U/mL IMA had 80% sensitivity and 31% specificity for diagnosing ischemia and an NPV of 92% (the same group had a myoglobin/CK-MB/troponin I panel sensitivity of 57%). When IMA was combined with the myoglobin, CK-MB and troponin I, the sensitivity rose to 97% for ischemia, and the NPV remained at 92% (34). Kazanis *et al*. also demonstrated that IMA correlated with increased risk of coronary artery disease and, at a cutoff of 101.5 KU/L, has a sensitivity and a specificity of 87.7% for coronary artery disease (35). In this same study, IMA had an NPV of 83.3% (35).

The utility of IMA in the ED requires more data, but according to recent data, IMA in the combination with other cardiac biomarkers may be very useful when evaluating patients with symptoms of cardiac ischemia and without evidence of cardiac necrosis (36).

Heart-type fatty acid binding protein (H-FABP)

H-FABP is a 14-kDa molecule involved in fatty acid transport, contained in the cytoplasm of cardiomyocytes, and tens of times more prevalent in cardiac muscle than skeletal muscle. It is released in the circulation around 30 min after myocardial injury, measurable within 1–3 hours in serum and within 1–2 hours in urine, and levels normalize within 12–24 hours (27). It is an early marker for cardiomyocyte ischemia and allows detection of injury prior to conventional markers of necrosis. It is commercially available for use only in some countries in Europe and Asia (27).

Okamoto *et al*. demonstrated that H-FABP in patients 12 hours after initiation of symptoms of cardiac ischemia has a sensitivity of 92.9%, specificity of 67.3% and diagnostic validity assessed by the area under the curve (AUC) of 0.921 for AMI (37). This was in comparison to the sensitivity of 88.6% for myoglobin and 18.6% for CK-MB, specificity of 57.1% for myoglobin and 98.0% for CK-MB, and AUC of 0.843 for myoglobin and 0.654 for CK-MB in comparison in the same study. These parameters showed similar findings in patients within 3 hours and 6 hours of initiation of symptoms (37). Liao *et*

al. also demonstrated that in patients with median length of symptoms of 2 hours, H-FABP had a sensitivity of 83.3% for AMI, the highest compared to conventional markers (38). While in the same study, cTnI had the highest specificity of 50.0% for AMI. They also found H-FABP identified AMI significantly earlier than cTnI (38). In addition, H-FABP also seems to be prognostic for the risk of adverse cardiovascular events (death, congestive heart failure, and recurrent MI) (27).

Inflammatory Biomarkers

C-reactive protein (CRP)

There is growing attention on C-reactive protein (CRP) as a biomarker in coronary artery disease. It is a known marker for systemic inflammation but like myoglobin not specific to cardiac injury. CRP elevations in coronary artery disease seem to be demonstrating that atherosclerosis is not only a marker of lipid accumulation but also of chronic inflammatory disease (39). Elevated CRP level has been associated with increased risk of MI, stroke, peripheral artery disease, sudden cardiac death. It has been associated with recurrent ischemia and death in those with stable and unstable angina, in those having percutaneous angioplasty, and in those with acute coronary syndrome (39). Studies have shown that high sensitivity CRP levels <1, 1–3, and >3 are low, moderate, high-risk groups, respectively, for future prognostic cardiac adverse event (39). In fact, CRP is a stronger predictor of cardiac events than LDL lipids (39).

CRP is highly stable and standardized in available commercial tests (39). It has a half-life of 18–20 hours (39). The limitation of CRP in the acute setting is its uncertain clinical cutoff points and timing for CRP levels in relationship to the onset of ischemia (39). There is no standardized method in CRP use. However, it is probable that CRP is most useful in the emergency room in helping the clinician decide in conservative or more aggressive management in those patients with ischemic symptoms but negative troponins (39).

Myeloperoxidase (MPO)

MPO is a leukocyte enzyme secreted in acute inflammation and causes oxidation of lipoproteins, which are involved in CVD (4). Not only does MPO predict the presence of coronary artery disease, it also seems to correlate the presence of acute coronary syndrome in patients with chest pain (4). Rudolph *et al*. showed that ED patients with chest pain, with MI had significantly higher MPO than patients without MI (40). Further, MPO was elevated in patients who eventually were diagnosed with MI, but initially had negative troponins (40). Overall, MPO had an NPV of 85.5% for AMI compared to that of TnI of 91.7% and MPO had a sensitivity of 80.0% for AMI compared to the sensitivity of TnI of 85.9% (38). For patients with symptom onset of ≤2 hours, the NPV of MPO increased to 95.6% compared to the NPV of TnI, which dropped to 73.3%. The sensitivity of MPO increased to 95.8%, while the sensitivity of TnI decreased to 50.0% (40). Brennan *et al*. also demonstrated that MPO levels in ED patients with chest pain significantly predicted the risk of MI even with initial negative troponins (41). MPO at presentation also predicted risk for MI, need for revascularization and death at 30 days and 6 months (41). As a result, the role of MPO in the ED is in risk stratification.

The limitation of MPO is in its nonspecificity. It is implicated in number of disease processes including atherosclerosis, MI, multiple sclerosis, Alzheimer's, malignancy, etc. (42). There also seems to be a lack of validation and standardization of MPO levels in current assays, which will need to be studied further prior to widespread use in ED (42).

Other inflammatory biomarkers including pregnancy-associated plasma protein and matrix metalloproteinase-9 are implicated in plaque rupture. There is limited data for these investigational biomarkers and further conclusive data is needed for definitive utility of these biomarkers in the future (4,27).

Markers of Blood Vulnerability

D-Dimer

D-dimer is a fibrin split product. It is formed as a result of the fibrinolysis pathway that breaks down fibrin and fibrinogen via plasmin into fibrin split products (4). The use of D-dimer in the ED is commonly used in ruling-out PE or deep venous emboli (DVT), especially those with low or moderate pretest probability in order to avoid CT pulmonary angiogram (4). Wells *et al*. showed that managing patients with suspected PE based on pretest probability and D-dimer was safe. Their study showed an NPV of 99.5% of this combined strategy (43). D-dimer is helpful when negative to rule out thromboembolic disease. However, D-dimer can be positive in a variety of diseases and physiological states, so it is nonspecific when levels are elevated. D-dimer levels may be elevated with age, trauma, pregnancy,

inflammation, malignancy, etc. (44).

Recent studies also have shown that D-dimer is elevated in AMI and acute aortic dissection. Sakamoto *et al*. showed that in patients presenting with chest pain, D-dimer values were significantly elevated in patients with acute aortic dissection 32.9 ± 66.7 g/mL, $p<0.001$, PE 28.5 ± 23.6 g/mL, $p<0.001$, and AMI 2.1 ± 3.7 g/mL. A cutoff level for D-dimer of 5.0 g/mL was 68% sensitive and 90% specific for differentiating AMI versus PE or acute aortic dissection (45). Sodeck *et al*. demonstrated that a D-dimer level of <0.1 µg/mL had an NPV of 100% for acute aortic dissection and suggested routine use to rule out acute aortic dissection (46).

The concern with D-dimer is that it is not specific for one disease process and current assays are very different from one another. Diverse cutoff values and lack of reference standardization makes D-dimer assays difficult to compare (44).

Other Coagulation Biomarkers

Fibrinogen and prothrombin fragments, like D-dimer, are part of the coagulation cascade, and elevated in AMI patients with possible prognostic utility. However, there is still a lack of definitive data on the extent of their clinical use for diagnostic and treatment purposes (6).

Platelets

Platelet activation is related to thrombosis in acute coronary syndrome. Several biomarkers have been tested to better assess the state of platelet activation.

von Willebrand's factor (vWF)

vWF is a glycoprotein that mediates platelets adhesion, platelet aggregation and is a carrier for factor VIII (47). It has a weak association with the general population but in those with previous vascular disease, vWF is predictive of morbidity and mortality (47). Koprivica *et al*. showed that the sensitivity of vWF activity test was 53.91%, while specificity was 97.5% for acute coronary artery disease (47). The sensitivity of vWF antigen test was 86.0%, while specificity was 100% for acute coronary artery disease (47). They suggested routine vWF testing in patients with acute coronary disease and using it as therapeutic target (47). Goto *et al*. showed that the high shear induced platelet aggregations in AMI is likely due to increased concentration of vWF (48). Yamashita *et al*. demonstrated that occlusive thrombi in rapid closure of coronary arteries were consistently made of vWF, fibrin, tissue factor and platelet (49). Glycoprotein IIb/IIIa and fibrin were associated with vWF and tissue factor, respectively, in this study. The authors suggested that vWF and tissue factor could be therapeutic targets (49). This central role of vWF in the process of thrombogenesis has made it a target for therapeutic intervention in patients with acute coronary disease (47). Ray *et al*. showed that in STEMI patients, the measured rise in vWF of ≥75th percentile had a 11.2% incidence of death and MI at 30 days compared to 4.1% for patients with vWF <75th percentile (50). They showed that enoxaparin independently lowered the measured rise in vWF levels and lowered the composite of death or MI (50).

vWF is not a biomarker readily available in the ED and its role in the acute ED setting would need to be investigated further for any added benefit over current cardiac biomarker panel.

New biomarkers are emerging for better discrimination of diagnosis, prognosis and treatment of cardiac disease (6). Other markers of platelet activation including CD40L, platelet neutrophil coaggregates, vsCAM-1, P-selectin, and platelet microparticles are being evaluated as well for their utility in the process of cardiac ischemia and necrosis (6,27). Growth factors like vascular endothelial growth factor, placental growth factor and hepatocyte growth factor are platelet-derived proteins involved in inflammatory process and atheroma formation. They are currently being investigated and have shown incremental prognostic value in acute coronary syndrome (4,27).

Final Thought

Biomarker use in the field of medicine is growing rapidly and so is the number of biomarkers available for use. They have become a part of the clinical workup of certain patients depending on the presenting symptoms, their history and physical. In the ED, time is of the essence and biomarkers have become gold standard in the workup of AMI and heart failure due to their diagnostic and prognostic value, cost effectiveness, and testing efficiency. As this article makes evident, no one biomarker has the specificity or sensitivity to be used independently. Therefore, a multiple biomarker approach strategy is recommended as the safest method of practice for clinicians in the workup of cardiac disease (4,6,27). Sabatine *et al*. demonstrated that the multiple biomarker approach to evaluate patients with symptoms of coronary artery disease markedly added prognostic value. They measured presenting BNP, TnI and CRP in patients with acute coronary syndrome and found that

each were predictive of composite of death, MI and CHF (51). What was important about this study was that with each additional biomarker that was elevated, there was a near doubling of death and similar findings for MI and CHF at 30 days to10 months (51). Patients with one elevated biomarker had a 2.1 times the risk of death, MI or CHF by 6 months (51). Those with two elevated biomarkers had 3.1 times the risk, and those with three elevated biomarkers had 3.7 times the risk of death, MI or CHF by 6 months (51). This additive approach has been evaluated in other studies as well, but there is no definitive approach or algorithm that has been established. There are many new cardiac biomarkers with promising prognostic and diagnostic data, but their availabilities are varied and more studies are needed to evaluate the multimarker approach (52). It is important for the clinician to keep in mind their patient demographics, cost-effectiveness of the biomarkers, each biomarker sensitivity/specificity, and use them in a way that would be best for their patients. The AHA guidelines are of course helpful in practice and as new data is presented, we will hopefully be able to use newer biomarkers in our maker panels to improve diagnostic, prognostic and therapeutic approaches.

Conflict of interest

Alan Maisel, consultant, Alere, Critical Diagnostics, EFG. Research support: Alere, Abbott, Nanosphere, Brahms-thermofisher, Novartis.

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