SIGNA VITAE 2017; 13(1): 89-94

The utility of point-of-care biomarkers as a prognostic tool for patients with acute coronary syndromes

YOUNG-DUCK CHO[1], SUNG-WOO LEE[2], YOUNG-HOON YOON[1], JUNG-YOUN KIM[1], JONG-HAK PARK[1], SUNG-HYUK CHOI[1]

1 Department of Emergency Medicine, Korea University Guro Hospital, Gurogu, Seoul, Korea
2 Department of Emergency Medicine, Korea University Anam Hospital, Sungbukgu, Seoul, Korea

Corresponding author
Sung-Woo Lee
Department of Emergency Medicine
Korea University Anam Hospital
Inchonro 73, Sungbukgu, Seoul 02841, Korea
Phone: 02-2626-1561
Fax: 02-2626-1562
E-mail: lukezax71@gmail.com

ABSTRACT

Introduction. Patients with symptoms suggestive of acute coronary syndrome (ACS) have various medical backgrounds and different stages of underlying coronary disease. Hence, patients entering the emergency room (ER) with ACS suggestive symptoms, present a challenge to emergency physicians. We hypothesized that a point-of-care test (POCT) for multiple cardiac biomarkers can be used as a prognostic tool for predicting severity and hospital mortality in acute myocardial infarction (AMI) patients.
Methods . We conducted a retrospective analysis of all patients who presented to the ER of a university urban hospital with chest pain, chest discomfort and shortness of breath of potential cardiovascular origin during a 3-year period. Biomarkers from the POCT and coronary angiography (CAG) results were used for diagnosis. Severity was evaluated based on involvement and status of major coronary arteries, ejection fraction and in-hospital mortality.
Results. Out of 1336 patients, 329 patients were diagnosed with AMI. Risk of major coronary artery occlusion was increased with an increased number of positive POCT findings. The percentage of patients with severe left ventricular dysfunction was higher in the group with 2 or 3 positive POCTs than 0 or 1. As the number of positive POCTs increased from 1 to 3, our results showed an increment in the percentage of in-hospital mortality
Conclusions. This study identified the possibility of a POCT as a prognostic tool. The POCT is easy to use by the bedside and can be checked relatively quickly? in a short period of time. If the POCT result is used to predict the prognosis in ACS patients, emergency physicians may approach patients with more caution.

Key words: chest pain, shortness of breath, acute myocardial infarction, in-hospital mortality

INTRODUCTION

Chest discomfort, pain and tightness with or without shortness of breath are always challenging symptoms for emergency physicians. Chest pain is one of the commonest reasons for admission to the emergency room (ER). Common causes include stable angina, gastrointestinal disease, panic disorder, viral infection and musculoskeletal pain. The most serious causes are acute coronary syndrome (ACS), heart failure (HF) and thromboembolic events (TE). (1-3) Patients with symptoms suggestive of ACS have various medical backgrounds and different stages of underlying coronary disease. Hence, patients entering the ER with ACS suggestive symptoms present a diagnostic, prognostic and therapeutic challenge. ACS is divided, based on electrocardiogram (ECG) findings, into ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The disruption of an atherosclerotic plaque and thrombus formation, causing partial or complete occlusion of the infarct-related artery or distal embolization in the coronary vessel, are key events of ACS development. (4) Many biomarkers are available for the diagnosis of ACS and utility of biomarkers may be used for diagnosis, prognosis and selection of appropriate treatment. (5,6) Also, the utility of biomarkers can be used essentially in risk stratification and diagnosis of acute myocardial infarction (AMI). (7,8) The most frequently used biomarkers are cardiac troponin T (cTnT) or cardiac troponin I (cTnI), brain natriuretic peptide (BNP) and D-dimer. (9) Additionally, creatine kinase MB (CK-MB) and myoglobin are used as adjuvant tests. CTnI or cTnT is a highly specific and sensitive protein for the diagnosis of ACS. (10,11) Elevated troponin due to myocardial necrosis is probably the result of a complex, thrombotic coronary lesion. (12,13) BNP identifies cardiac origin dyspnea and excludes heart failure (HF) in an ACS suspected patient. (14) Cardiac ventricles' increased wall tension leads to release of BNP and the N-terminal part of its pre-hormone (NT-proBNP) from myocytes. (15) Although BNP and NT-pro-BNP are widely used for the diagnosis of HF, many studies show an elevated level of BNP in the early stage of ACS. It has also been shown to be a strong indicator of mortality in ACS patients. (16,17) D-dimer is a degradation product of cross-linked fibrin and it is elevated in the presence of an acute clot due to simultaneous activation of coagulation and fibrinolysis. (18-20) Plasma D-dimer is useful for the exclusion of pulmonary embolism (PE) and deep vein thrombosis (DVT). (21) Its specificity is usually low given that it is elevated in numerous non-thrombotic situations. (22) With a high sensitivity and high negative predictive value, D-dimer functioned as a great screening tool for suspected PE. However,

D-dimer was often elevated in the absence of PE. It had a low specificity and poor positive predictive value. (22-28)

In this study, we hypothesized that the point-of-care test (POCT) for multiple cardiac biomarkers can be used as a prognostic tool for estimating the severity and in-hospital mortality of AMI patients. In other words, the occlusion of the left main coronary artery, number of involved coronary arteries and the ejection fraction (EF) of the left ventricle (LV), may be used as factors that reflect the severity of AMI. Our aim was to analyze the utility of the POCT of multiple cardiac biomarkers for risk stratification in the setting of an emergency department.

METHODS

We conducted a retrospective analysis of all patients who presented to the ER of an urban university hospital with chest pain, chest discomfort and shortness of breath, of potential cardiovascular origin, during a 3-year period (January 2013 to December 2015). We reviewed the electronic records of all patients. Patients diagnosed with AMI, based on the International Classification of Diseases, tenth Revision (ICD-10) code 29, POCT multiple cardiac biomarkers findings and coronary angiography (CAG) results,, were included in our study. General demographics, initial vital signs, POCT results, ejection fractions, CAG results and in-hospital mortalities were collected from the sample. Severity was evaluated based on involvement of the left main coronary artery, number of involved coronary arteries, ejection fraction from a 2 dimensional cardio-echogram and in-hospital mortality. Shortness of Breath (SOB) kit (Alere TM Triage® Meter-Pro, Allere Inc. San Diego, CA. USA) was used for biomarker testing. Five biomarkers, previously mentioned, were assessed using fluorescence immunoassay by placing 0.5mg of patient's whole blood onto the kit. The time required for the kit to analyze the blood sample is about 10~15 minutes. Standard values for each biomarker are set to the manufacturer's normal ranges and they are: CK-MB 0.0 – 4.3 ng/mL, Myoglobin 0.0 – 107 ng/mL, Tnl < 0.05 ng/mL, BNP 0.0 – 100 pg/mL, D-dimer 0.0-400 ng/mL respectively. If measurement of Tnl reaches between 0.05 – 0.39 ng/mL, it is considered slightly abnormal and if it is over 0.4 ng/mL, it is definitely abnormal, according to the manufacture.

After reviewing patients' final diagnosis, AMI, heart failure and pulmonary embolism were defined as representing acute coronary vascular diseases. AMI is defined as more than one of following: elevation of serum CK-MB or Troponin during hospital stay, ischemic change in electrocardiogram (EKG), newly found impaired wall motion in 2-dimensional echocardiogram (2-D Echo) and confirmed coronary artery occlusion in CAG. Patients with more than 70% stenosis in one of the three major arteries, including the left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) or in their first-order branches were eligible for percutaneous coronary intervention (PCI). Therefore, occlusion of more than 70% of major arteries was considered to be involved. Clinical symptoms suspicious of heart failure and decreased ejection fraction on 2-D Echo were needed to diagnose heart failure. Ejection fraction (EF) above 55% was considered normal, between 45~54% was considered moderate and below 45% was considered severe. Pulmonary embolism was diagnosed when an embolus was confirmed on 64 channel computed tomography (CT). In-hospital-mortality was defined as a final prognostic index and it was collected for each acute coronary vascular diseases. Chi-square test was used to analyze the relationship between initial elevation of Tnl, BNP and D-dimer and the prognosis of each disease in the group of patients who were diagnosed with AMI and heart failure. In the pulmonary embolism group, the difference in mortality, depending on initial elevation of Tnl and BNP, was analyzed in the same manner. Initial measurement of Tnl was subdivided into < 0.05ng/mL, 0.05 – 0.39 ng/mL, and > 0.40 ng/mL and the effect of the result on prognosis was analyzed. All statistical analyses were conducted using SPSS 10.29 (IBM Inc. Armonk, NY).

This study was approved by the Institutional Review Board (IRB) of the Korea University Guro Hospital.

Approval number is KUGH16262-001

RESULTS

A total of 1336 patients were tested with POCT for multiple cardiac biomarkers; 329 patients were diagnosed with AMI. Two patients died before enrollment into the study due to cardiac arrest at presentation. Among the 329 patients, CAG was done on 280 patients. Among the CAG group, 17 patients died and 263 were discharged alive (figure 1).

General characteristics and information about the study group are shown in Table 1. Average age was 58 ± 16 years and male patients were more common than female (64.3% vs. 35.7%). Chest pain was the most common symptom and angina pectoris (including other forms of angina pectoris) was the most common final diagnosis, followed by AMI and unstable angina.

17 patients died within 30 days of CAG, and 263 patients were discharged alive. Analysis of the expired and survival group, showed expired patients to be older (72±8 vs. 58±13 years, P<0.001) and have a lower systolic blood pressure (103±24 vs. 132±26 mmHg, P<0.001). Initial biomarker levels, Tn-I (16.0(0-30) vs. 1.4(0-3.0) ng/mL [CI], P<0.001), BNP (532(125-1180) vs. 31(5-215) pg/mL [CI], P<0.001) and D-dimer (567(259-1535) vs. 119(100-393) ng/mL [CI], P<0.001) were higher in the expired group compared to the survival group. On CAG findings, mortality was higher when more coronary arteries were occluded (P=0.005) (table 2).

The risk of left main coronary artery occlusion increased with the number of positive POCTs. When three POCT were positive, the percentage of involvement of the left

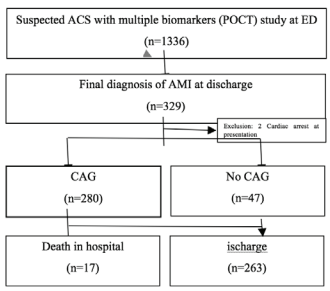

Figure 1. Selection of study population ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; CAG, Coronary angiography; POCT, Point-of-care test.

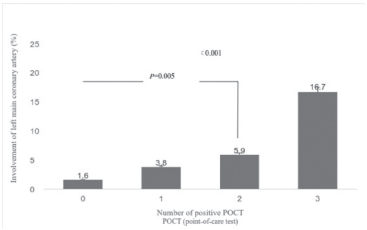

Figure 2. Involvement of left main coronary artery in relation to number of positive POCT.

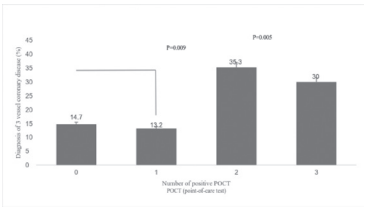

Figure 3. Percentage of 3 vessel coronary disease in relation to number of positive POCT

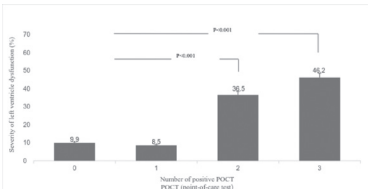

Figure 4. Severity of left ventricular dysfunction in relation to number of positive POCT

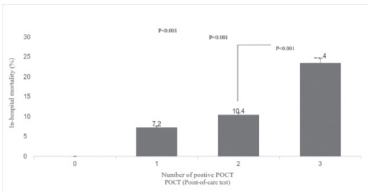

Figure 5. In-hospital mortality rate in relation to number of positive POCT

main coronary artery was increased 10 fold (1.6% to 16.7%, P<0.001). The risk increased more than 3 times with 2 positive POCT compared to none (1.6% to 5.9%, P=0.005) (figure 2).

The risk of 3 vessel coronary artery disease in patients with 2 and/or 3 positive POCT vs patients with 0 and/or 1 positive POCT was 35.3% and/or 30% vs. 14.7% and/or 13.2%, P=0.005, respectively (figure 3).

To verify the severity of left ventricular dysfunction, we sought to compare the percentage of patients with EF below 45% with the number of positive POCTs. The percentage of patients with severe left ventricular dysfunction was higher in 2 or 3 positive POCTs than 0 or 1 (36.5% or 46.2% vs. 9.9% or 46.2%, P<0.001) (figure 4).

In-hospital death was not noticed in the group with no positive POCT. However, as the number of positive POCTs increased from1 to 3, our results showed an increment in the percentage of in-hospital mortality (7.2%, 10.4%, 23.4% respectively, P<0.001) (figure 5).

Table 1. Baseline characteristics of study patients

Characteristics	Values
Age (mean ± SD, years)	58 ± 16
Male : Female (%)	859:477 (64.3% : 35.7%)
Initial symptoms	
Chest pain, n (%)	972 (72.8)
Dyspnea, n (%)	289 (21.6)
Chest pain + dyspnea, n (%)	75 (5.6)
Final diagnosis	
Acute myocardial infarction, n (%)	329 (24.6)
Congestive heart failure, n (%)	165 (12.4)
Pulmonary embolism, n (%)	17 (1.3)
Unstable angina, n (%)	156 (11.7)
Other Angina pectoris, n (%),	441 (33.0)
Arrhythmia, n (%)	27 (2.0)
Myocarditis, n (%)	14 (1.0)
Myopathy, n (%)	11 (0.8)
Aortic dissection or aneurysm, n (%)	17 (1.2)
Pulmonary disease, n (%)	53 (4.0)
Others, n (%)	106 (7.9)

DISCUSSION

Accurate and early diagnosis of AMI in patients with related symptoms improves clinical outcome and prognosis. Moreover, determining the prognosis of AMI is essential for triaging patients in the setting of limited resources in the ER.

The use of plasma biomarkers has become central to the diagnosis and management of acute coronary syndromes and exclusion of myocardial necrosis. (29) Specifically, the diagnostic value of troponin I or T (TnI or TnT) elevation among patients with myocardial infarction (MI) is well established. (30,31) Long-term mortality and morbidity following MI are largely determined by infarct size, and the extent of left ventricular (LV) dysfunction. (32) In our study, AMI patients who took longer to get to the ER from symptom onset, who were older and who were hypotensive at arrival were more likely to have a poor prognosis. Furthermore, other studies have shown that biomarkers are not just used for diagnosis but for prediction of prognosis. (33-35) However, they only showed the utility of each biomarker for prognosis of specific disease.

We believe that if these biomarkers are positive, the chance of involvement of the left main coronary artery, three-vessel coronary artery disease and left ventricular dysfunction will increase. Regardless of biomarker type, an increase in the number of positive biomarkers correlated with an increase in in-hospital mortality in our study. Eventually, this result will lead to higher in-hospital mortality. Given that the number of positive biomarkers is closely related to a higher risk of three coronary vessel disease, it may be useful in predicting the possibility of surgical treatment, such as coronary artery bypass graft surgery (CABG), rather than coronary angiography alone.

This was a retrospective study. Hence, there were some limitations. First, initial results of biomarkers were not able to predict incidence and mortality of acute coronary vascular disease. Only data from patients with a final diagnosis of AMI, heart failure, and pulmonary embolism were analyzed and data from general patients complaining of cardiovascular symptoms such as chest pain or shortness of breath were not able to be analyzed for risk stratification.

Table 2. Baseline characteristics of analyzed patients for death in hospital group and discharged alive group (N=1336)

Characteristics	Death in hospital (n = 17)	Discharged alive (n = 263)	p-value
Age (mean ± SD, years)	72 ± 8	58 ± 13	< 0.001
Male (%)	5 /17 (29.41%)	53 /263 (20.15%)	0.360
Initial symptoms			
Chest pain, n (%)	12 (70.6)	218 (82.9)	
Short of breath, n (%)	**2 (11.8)**	**23 (8.7)**	
Chest pain + SOB, n (%)	**2 (11.8)**	**9 (3.4)**	
Epigastric & abdominal pain	**1 (5.9)**	**12 (4.6)**	
General weakness or altered state	**0 (0)**	**1 (0.4)**	
Symptom to presentation (hours)	**9.5 (2.2-36.0)**	**2.9 (1.0-12.1)**	**0.033**
Initial vital signs			
Systolic blood pressure (mmHg)	**103 ± 24**	**132 ± 26**	**< 0.001**
Diastolic blood pressure (mmHg)	**62 ± 27**	**80 ± 17**	**0.013**
Pulse rate (beat/min)	**77 ± 28**	**80 ± 19**	**0.689**
Respiratory rate (breath/min)	**21 ± 6**	**21 ± 3**	**0.893**
MAP < 70 mmHg, n (%)	**7 (41.2)**	**15 (5.7)**	**< 0.001**
Initial biomarkers			
CK-MB (ng/mL)	**37.0 (1.5-74.5)**	**4.0 (1.0-18.0)**	**0.010**
Myoglobin (ng/mL)	**144 (93-500)**	**153 (65-456)**	**0.287**
Tn-I (ng/mL)	**16.0 (0-30)**	**0 (0-2.0)**	**< 0.001**
BNP (pg/mL)	**532 (125-1180)**	**31 (5-215)**	**< 0.001**
D-dimer (ng/mL)	**567 (259-1535)**	**119 (100-393)**	**< 0.001**
EF at 2D-echo (n=257)	**n=10**	**n=247**	**0.258**
> 55%, n (%)	**1 (10.0)**	**86 (34.8)**	
45-55%, n (%)	**6 (60.0)**	**113 (45.7)**	
< 45%, n (%)	**3 (30.0)**	**48 (19.4)**	
CAG finding			
Left main involvement, n (%)	**3 (17.6)**	**10 (3.8)**	**0.036**
No. of involved coronary arteries			
1 vessel, n (%)	**2 (11.8)**	**127 (41.4)**	**0.005**
2 vessels, n (%)	**7 (41.2)**	**85 (32.3)**	**0.005**
3 vessels, n (%)	**8 (47.1)**	**51 (19.4)**	**0.005**

BNP, brain natriuretic peptide; CAG, Coronary angiography; CK-MB, Creatine kinase MB; 2-D Echo, 2-dimensional echocardiogram; EF, Ejection fraction; MAP, Mean arterial pressure; SOB, Shortness of breath; TnI, troponin I.

Second, due to the setting of in-hospital-mortality as a prognostic index, assessing risk stratification between patients with minimal elevation of Tnl and patients with a normal range of Tnl was not possible. Third, we assumed initial elevation of D-dimer in AMI patients was closely related to severe coronary vascular damage caused by a thrombus. In addition to that, visualization of thrombus formation by 2-D echo is required. Finally, a specific combination of biomarkers was not able to be identified. However, such information was not accessible due to the retrospective study design. In spite of the retrospective study design, this study confirmed that multiple biomarkers used in ER for differential diagnosis of acute cardiovascular disease also can be used as a prognostic risk stratification tool.

Our study identified the possibility of employing biomarkers from POCT as a prognostic tool. POCT is easy to use by the bedside and can be checked relatively ? in a short period of time. If the results from POCT is used to predict the prognosis of ACS patients, emergency physicians may approach patients with more caution. Prospective studies are required to assess the utility of multiple biomarkers in the ER for acute cardiovascular disease's incidence rate and for prediction of prognosis in patients with cardiovascular symptoms.

REFERENCES

1. Punukollu H, Khan IA, Punukollu G, Gowda RM, Mendoza C, Sacchi TJ. Acute pulmonary embolism in elderly: clinical characteristics and outcome. Int J Cardiol 2005;99:213-6.
2. Godfrey C, Harrison MB, Medves J, Tranmer JE. The symptom of pain with heart failure: a systemic review. J Card Fail 2006;12:307-13.
3. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest 2004;126:461-9.
4. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (second of two parts). N Engl J Med 1992;326:310-8.
5. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. J Am Coll Cardiol 2006;48:1-11.
6. Sciria BM. Acute coronary syndrome: emerging tools for diagnosis and risk assessment. J Am Coll Cardiol 2010;55:1403-15.
7. Fesmire FM, Decker WW. Diercks DB, Ghaemmaghami CA, Nazarian D, Brady WJ, Hahn S, Jagoda AS; American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Non-ST-Segment Elevation Acute Coronary Syndromes. Clinical policy: critical issues in the evaluation and management of adult patient with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med 2006;48:207-301.
8. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH, Apple FS, Francis G, Tang W; National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clin Chem 2007;53:552-74.
9. Harrison A, Amundson S. Evaluation and management of the acutely dyspneic patient: the role of biomarkers. Am J Emerg Med 2005;23:371-8.
10. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
11. Newby LK, Christenson RH, Ohman EM, Armstrong PW, Thomson TD, Lee KL, et al. Value of serial troponin T measures for early and late risk stratification in patients with acute coronary syndromes. The GUSTO-IIa Investigators. Circulation 1998; 98:1853-9.
12. Heeschen C, van Den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. Circulation 1999;100:1509-14.
13. Okamatsu K, Takano M, Sakai S, Ishibashi F, Uemura R, Takano T, et al. Elevated troponin T levels and lesion characteristics in non-ST-elevation acute coronary syndromes. Circulation 2004;109:465-70.
14. Januzzi JL, van Kimmenade T, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the international Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330-7.
15. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;6:257-60.
16. Wiviott SD, de Lemos JA, Morrow DA. Pathophysiology, prognostic significance and clinical utility of B-type natriuretic peptide in acute coronary syndromes. Clin Chim Acta 2004;346:119-28.
17. James SK, Lindhal B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. Circulation 2003;108:275-81.
18. Kearon C, Ginsberg JS, Douketis J, Turpie AG, Bates SM, Lee AY, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 2006;144:812-21.
19. Righini M, Perrier A, De Moerloose P and Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost 2008;6:1059-71.
20. Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: an overview. J Thromb Haemost. 1994;71:1-6.
21. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J 2005;26:1765-73.
22. Becattini C, Lignani A, Masotti L, Forte MB and Agnelli G. D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis 2012;33:48-57.
23. Goldhaber SZ, Simons GR, Elliott CG, Haire WD, Toltzis R, Blacklow SC, et al. Quantitative plasma D-dimer levels among patients undergoing pulmonary angiography for suspected pulmonary embolism. JAMA 1993;270:2819-22.
24. Abcarian PW, Sweet JD, Watabe JT, Yoon HC. Role of a quantitative D-dimer assay in determining the need for CT angiography of acute pulmonary embolism. AJR Am J Roentgenol. 2004;182:1377-81.
25. Kabrhel C, Mark Courtney D, Camargo CA Jr, Plewa MC, Nordenholz KE, Moore CL, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med 2010;17:589-97.
26. Kearon C, Ginsberg JS, Douketis J, Turpie AG, Bates SM, Lee AY, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 2006;144: 812-21.
27. Yin F, Wilson T, Della Fave A, Larsen M, Yoon J, Nugusie B, et al. Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism. Am J Med Qual 2012;27:74-9.
28. Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL and Goldhaber SZ. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. J Am Coll Cardiol 2002;40:1475-8.
29. Hamm CW, Ravkilde J, Gerhardt W, Jørgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable

angina. N Engl J Med 1992;327:146-50.
30. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342-9.
31. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. Heart 2008;94:730-6.
32. Omland T, Aakvaag A, Bonarjee VV, Caidahl K, Lie RT, Nilsen DW, et al. Plasma brain natriuretic peptides as an indicator of left ventricular systolic function and long term survival after myocardial infarction: comparison with plasma atrial natriuretic peptide. Circulation 1996;93:1963-9.
33. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, et al. A rapid bedside test for B-type peptide predicts treatment outcome in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001;37:386-91.
34. Giannitsis E, Müller-Bardorff M, Kurowski V, Weidtmann B, Wiegand U, Kampmann M, et al. Independent prognostic value of cardiac troponin T n patients with confirmed pulmonary embolism. Circulation 2000;102:211-7.
35. Tulevski II, Mulder BJ, van Veldhuisen DJ. Utility of a BNP as a marker for RV dysfunction in acute pulmonary embolism. J Am Coll Cardiol 2002;39:2080.