The Assessment of the Diagnostic Value of the Heart-Type Fatty Acid-Binding Protein (hFABP) in the Patients Suffering from Chest Pain and Suspected with Acute Coronary Syndrome

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Abstract. This research aimed to assess the diagnostic value of hFABP in diagnosing the AMI in patients with the chest pain onset ≤ 6 hours. This diagnostic study was performed on 39 patients with the chest pain onset ≤ 6 hours in the Emergency Room of Dr Wahidin Sudirohusodo hospital, Makassar from February 2015 through March 2015. The patients were divided into two groups: the AMI group and the Non-AMI group based on the WHO criteria within 12 hours after admission. Then, their diagnostic values, such as the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the hFABP and troponin T were calculated and compared. The research results revealed that the sensitivity, negative predictive value, and accuracy of the hFABP were higher than the troponin T (87.5 % vs 41.6%, 80% vs 51.7%, and 84.6% vs 64.1%, respectively). Of the 17 patients with the final diagnosis of the NSTEMI, 10 patients showed negative troponin T in the initial examination when they entered the Emergency Room. Of the 10 patients, 7 patients (70.0%) had positive hFABP in the initial examination at the moment they entered the Emergency Room. Such results indicated that examination of hFABP had sensitivity, negative predictive value, and higher accuracy compared to the troponin T in diagnosing the AMI onset of ≤ 6 hours. In the patients with the early onset of chest pain with ECG non-ST elevation and negative troponin T, the hFABP could be used to predict the incidence of AMI.

Keywords: Acute Myocardial Infarction, hFABP, Troponin T.

1 Introduction

Acute coronary syndrome (ACS) is a spectrum of clinical syndromes ranging from unstable angina pectoris, acute myocardial infarction (ST elevation and non ST elevation) to sudden death. Acute myocardial infarction was diagnosed based on WHO criteria including the presence of typical chest pain complaints, changes in the ECG

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picture, and an increase in cardiac biomarkers [1]. The incidence of ACS is increasing every year. In the United States, more than 13 million people suffer from coronary heart disease (CHD), and approximately 1.4 million ACS sufferers must be hospitalized each year. Approximately 150,000 Americans are diagnosed with unstable angina each year [2]. In China, in 2007, a total of 22,130 patients were admitted to the emergency department of FuWay Hospital, which is a cardiovascular institution because of cardiovascular disease [3]. In Indonesia, based on Basic Health Research in 2007, deaths from cardiovascular disease (stroke and coronary heart disease) were ranked first [4].

Diagnosing ACS patients earlier is a challenge for doctors, especially doctors who work in the emergency department (ER). Errors or delays in diagnosing cases of ACS can increase patient morbidity and mortality. Conversely, diagnosing ACS earlier will reduce morbidity and mortality [5]. Most ACS patients come to the ER with complaints of chest pain, which occupies about 5% of all visits to the ER. To determine whether the chest pain is cardiac chest pain or not is a challenge for a doctor, especially in patients who come with atypical chest pain [6]. Although the electrocardiogram (ECG) is the leading diagnostic tool for detecting ACS, it has a low sensitivity (35-50%), so that normal EKG results do not necessarily rule out ACS [3, 7]. Under these conditions, cardiac biomarkers (troponin T or I and CKMB) play an important role in establishing the diagnosis of ACS. However, these biomarkers have not increased significantly at the onset of less than 4-6 hours, so clinicians still need time to wait until the blood sample is adequate for testing these biomarkers. Most of these cases must be observed for 10-12 hours, so that besides causing a stagnation of patients in the ER, a late diagnosis will also cause greater complications for the patient [8]. For this reason, biomarkers are needed as necrosis markers that are more sensitive and can be detected more quickly in the blood, so the doctors can diagnose ACS more quickly.

To answer this challenge, in the last 20 years, many studies have been conducted on Heart-type fatty acid-binding protein (hFABP) as a biomarker for ischemic heart muscle [9], introduced hFABP as a new biomarker for acute myocardial infarction. Heart-type fatty acid-binding protein is a small cytosolic protein that is abundant in cells with active fatty acid metabolism such as heart muscle [10]. HFABP levels begin to increase after 30 minutes to 1 hour after ischemic onset and reach a peak in 3-6 hours, then return to normal within 24-30 hours [11, 12]. The hFABP examination process is also quite simple, which can be done beside the patient using strips and the results can be obtained in less than 10 minutes. This study aims to evaluate the diagnostic value of hFABP in diagnosing AMI in patients with chest pain onset $\leq$ 6 hours.

2 Materials and Methods

2.1 Location and Research Design

This study was conducted at the Emergency Unit of Dr. Wahidin Sudirohusodo Hospital, Makassar, from February 2015 to March 2015. This study is a diagnostic test

to evaluate the diagnostic value of hFABP in diagnosing AMI in patients with chest pain onset ≤ 6 hours.

2.2 Population and Sample

The population of this study were all chest pain patients with suspected ACS onset ≤ 6 hours. The sample of this study were all chest pain patients with suspected ACS onset ≤ 6 hours who were admitted to the ER of Dr. Wahidin Sudirohusodo Makassar, during the study period, who met the inclusion and exclusion criteria. Samples were taken by consecutive sampling until the desired number of samples was reached.

A total of 39 patients with complaints of typical chest pain who met the inclusion and exclusion criteria from February to March 2014 were included in this study. The inclusion criteria included chest pain patients suspected of ACS onset ≤ 6 hours and willing to participate in the study by signing informed consent. The exclusion criteria included patients with a history of muscle trauma, including intramuscular injection within 3 days, had undergone percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) in the last 30 days, had suffered from IMA within the previous 30 days, ADHF, suffering from renal impairment, patients with hypertensive crisis, patients with severe illness, such as cardiogenic shock or sepsis, or acute ischemic stroke.

2.3 Method of Collecting Data

All patients with chest pain with suspected ACS onset ≤ 6 hours were subjected to routine triage checks as soon as possible. ECG examination done in less than 10 minutes. Patients who met the inclusion and exclusion criteria were then given informed consent, 3 ml of venous blood was taken for hFABP and troponin T examination. Patients with negative troponin T test results will be subject to serial examinations within 6-12 hours later. The final diagnosis of AMI or unstable angina pectoris using WHO criteria was made within 12 hours after the patient entered the ER. Patients were then grouped into two (based on WHO criteria), namely the AMI group (myocardial infarction with ST-segment elevation and myocardial infarction without ST-segment elevation) and the non-AMI group (unstable angina pectoris).

All patients underwent comprehensive interviews to obtain information about their current medical history, past medical history, risk factors for CHD, and family history of CHD. Demographic data and clinical data were recorded which included age, sex, and CHD risk factors, and the results of laboratory tests were recorded, including random blood sugar, SGOT/SGPT, urea, creatinine, lipid profile, the data of which was taken from medical records, interview with the patient or the patient's family. The research flow can be seen in Fig. 1.

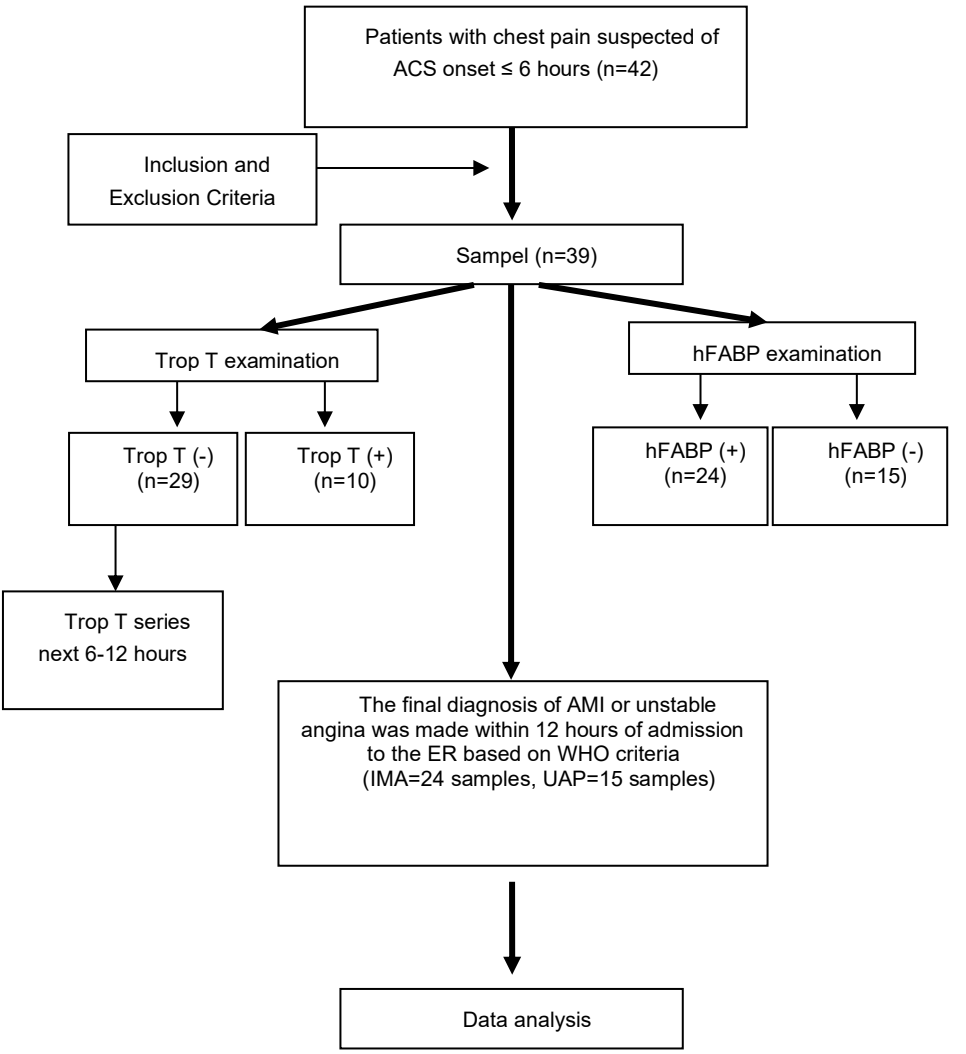

Fig. 1. Research flow.

2.4 hFABP Examination Procedure

Examination of hFABP levels using *Quicksens*^{R}. The examination material used is venous blood with heparin anticoagulant. The principle of this examination is the immunological method using the rapid chromatographic immunoassay method. In the cartridge there are 2 types of specific hFABP monoclonal antibodies, namely specific anti-hFABP conjugated with a substance labeled gold in the area after the sample site and specific anti-hFABP in the detection area.

Procedure for testing hFABP: Place 4 drops (100 μL) of blood in the sample holder in the cartridge. Samples flowed capillaryly through gold-labeled anti-hFABP sites.

Gold-labeled anti-hFABP will detach from its site and form a complex with hFABP if hFABP is present in the specimen. The complex will pass through the detection area and form a sandwich complex with the anti-hFABP that is there. This sandwich complex will give a red line (positive result). If there is no hFABP in the sample, a sandwich complex will not form so that a red line is not formed (negative result). So the qualitative results can be read visually.

2.5 Troponin T Examination Procedure

The examination material used is venous blood with heparin anticoagulant. The principle of this examination is the immunological method with the sandwich method. Procedure for testing cTrop-T: Pipette 150 ul of sample into the sample holder above the test strip. Press the start button of the cardiac reader tool then insert the test strip in its place on the cardiac reader. The tool will count down and then when it is finished calculating the results will appear on the screen.

2.6 Data Analysis

For data with a nominal scale presented in the form of frequency. Chi-square is used to see the differences in characteristic data in the two groups. The diagnostic ability of hFABP and troponin T assays is determined by calculating the sensitivity and specificity, NPP, and NPN, and their accuracy. All data obtained was analyzed via computer using the Statistical Package for Social Science (SPSS) version 16.0. The results obtained will be displayed in narrative form supplemented by tables or pictures. The data is declared significant if the p value <0.05.

3 Results

During the study period, 42 samples were collected that met the inclusion criteria, but 3 samples were excluded due to impaired renal function (eGFR <60 ml/hour). Of the 39 samples, 24 samples (61.5%) were AMI patients and 15 samples (38.5%) were non-AMI patients (unstable angina pectoris). Most of the onset when subjects entered the ED was ≤ 3 hours, which was 31 subjects (79.5%), while onset > 3-6 hours was only 8 subjects (20.5%). A total of 36 subjects were male, 21 subjects in the IMA group and 15 subjects in the non-IMA group. The mean age of the subjects was 54.1 ± 9.3 years, with a range of 41-73 years. Most of the subjects were aged ≤ 55 years (59%), both in AMI patients (62.5%) and non-AMI patients (53.3%). A total of 22 study subjects suffered from hypertension, 12 subjects in the IMA group and 10 subjects in the non-IMA group. A total of 38 subjects (79.5%) had no previous history of CHD, 24 subjects were in the AMI group (95.8%) and 14 subjects were in the non-AMI group (53.3%). The majority (97.4%) of the subjects had no family history of CHD, either in the AMI group (100%) or the non-IMA group (93.3%). Most of the subjects also did not have a history of DM (76.9%), but more than half (51.3%) of subjects entered the hospital with a random blood sugar (RBS) level > 140 mg/dL, with an average RBS of

178.5 ± 98.2 mg/dL, with range between 87 mg/dL - 405 mg/dL. Average LDL 133.7 ± 30.3 mg/dL, with a range between 67 mg/dL-224 mg/dL, 20 subjects had LDL levels ≤ 130 mg/dL and 19 subjects had LDL levels >130 mg/dL. The average HDL level was 42 ± 12.6 mg/dL, with a range of values between 15 mg/dL – 97 mg/dL, 32 subjects had HDL levels ≤ 50 mg/dL and only 7 subjects had HDL levels > 50 mg/dL. The mean serum creatinine was 1.04±0.2 mg/dL with a range of values between 0.6 – 1.7 mg/dL, the majority of subjects (84.6%) had serum creatinine levels ≤ 1.2 mg/dL. The basic characteristics of research subjects can be seen in Table 1.

Table 1. Baseline characteristics of subjects.

Characteristics	n (%)	AMI (n=24) (61.5%)	Non AMI (n=15) (38.5%)	P*
Onset				
- ≤ 3 hours	31(79.5%)	18 (75%)	13 (86.7%)	0.450
- >3-6 hours	8(20.5%)	6 (25%)	2 (13.3%)	
Age				
- ≤ 55 y.o	23 (59%)	15 (62.5%)	8 (53.3%)	0.571
- > 55 y.o	16 (41%)	9 (37.5%)	7 (46.7%)	
Sex				
- Male	36 (92.3%)	21 (87.5%)	15 (100%)	0.271
- Female	3 (7.7%)	3 (12.5%)	0 (0%)	
Hypertension				
- Yes	22 (56.4%)	12 (50%)	10 (66.7%)	0.307
- No	17 (43.6%)	12 (50%)	5 (33.3%)	
Family history of CHD				
- Yes	1 (2.6%)	0 (0.0%)	1 (6.7%)	0.385
- No	38 (97.4%)	24 (100%)	14 (93.3%)	
History of CHD				
- Yes	8 (20.5%)	1 (4.2%)	7 (46.7%)	0.003
- No	31 (79.5%)	23 (95.8%)	8 (53.3%)	
History of DM				
- Yes	9 (23.1%)	6 (25%)	3 (20%)	1.000
- No	30 (76.9%)	18 (75%)	12 (80%)	
Random Blood Sugar				
- ≤ 140 mg/dL	19 (48.7%)	13 (70.0%)	6 (30.0%)	0.389
- > 140 mg/dL		11	9 (45.5%)	

	20 (51.3%)	(54.5%)		
LDL				
- ≤ 130 mg/dL	20 (51.3%)	11 (45.8%)	9 (60%)	0.389
- > 130 mg/dL	19 (48.7%)	13 (54.2%)	6 (40%)	
HDL		20 (83.3%)		
- ≤ 50 mg/dL	32 (82.1%)	4 (16.7%)	12(80%)	1.000
- > 50 mg/dL	7 (17.9%)		3 (20%)	
Obesity		5 (20.8%)		
- Yes	7 (17.9%)	19 (79.2%)	2 (13.3%)	0.686
- No	32 (82.1%)		13 (86.7%)	
History of smoking		16 (66.7%)		
- Yes	26 (66.7%)	8 (33.3%)	10 (66.7%)	1.000
- No	13 (33.3%)		5 (33.3%)	
Creatinin serum		22 (91.7%)		
- ≤ 1.2 mg/dL	33 (84.6%)	2 (8.3%)	11 (73.3%)	0.180
- > 1.2 mg/dL	6 (15.4%)		4 (26.7%)	

Source: Primary data on 2015
*Chi-square

Comparison of the sensitivity, specificity, positive predictive value, negative predictive value between hFABP and Troponin T in chest pain patients suspected of acute coronary syndrome onset ≤ 6 hours can be seen in Fig. 2. From the figure, it appears that the sensitivity, NPN, and accuracy of hFABP are higher higher than troponin T in chest pain patients with suspected acute coronary syndrome onset ≤ 6 hours (87.5% vs 41.6%, 80.0% vs 51.7%, and 84.6% vs 64.5%). However, troponin T specificity and NPP were higher than hFABP (80% vs 100% and 87.5% vs 100%).

Of the 24 samples with AMI, 7 samples showed ST elevation ECG (STEMI diagnosis) and 17 samples had non-ST elevation ECG images (NSTEMI diagnosis). All samples (100%) with a diagnosis of STEMI showed positive hFABP results and only 3 samples (42.8%) showed positive troponin T results. In samples with a final diagnosis of NSTEMI, only 7 samples (41.1%) showed positive initial troponin T results, while 10 samples (58.9%) showed negative initial troponin T results. As many as 7 out of 10 samples (70%) with negative troponin T initial examination results obtained positive hFABP examination (Fig. 3).

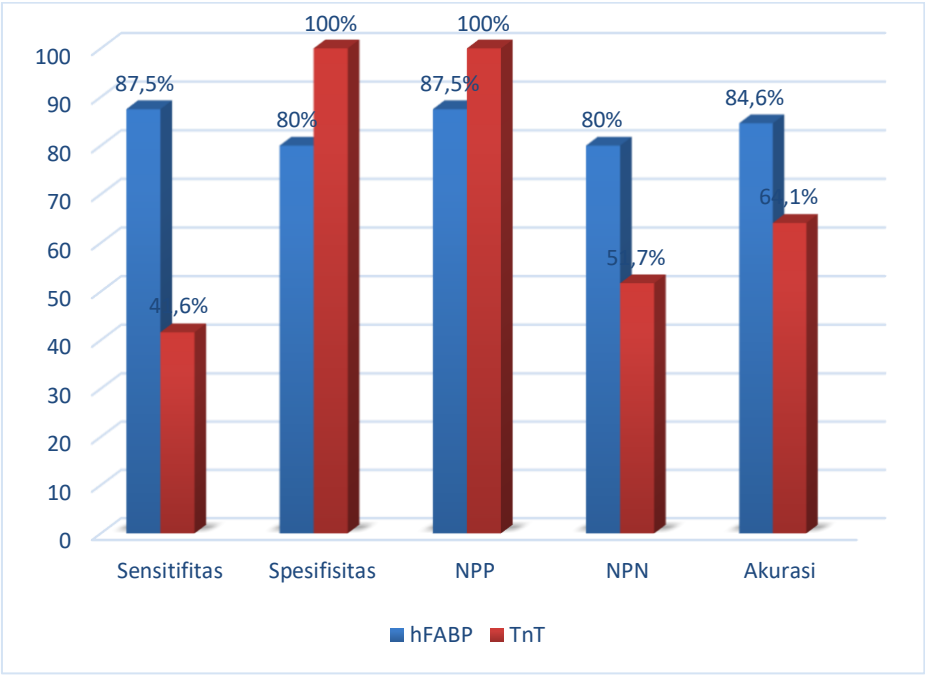

Fig. 2. Comparison of the diagnostic value between hFABP and TnT in chest pain patients with suspected acute coronary syndrome with an onset of ≤ 6 hours.

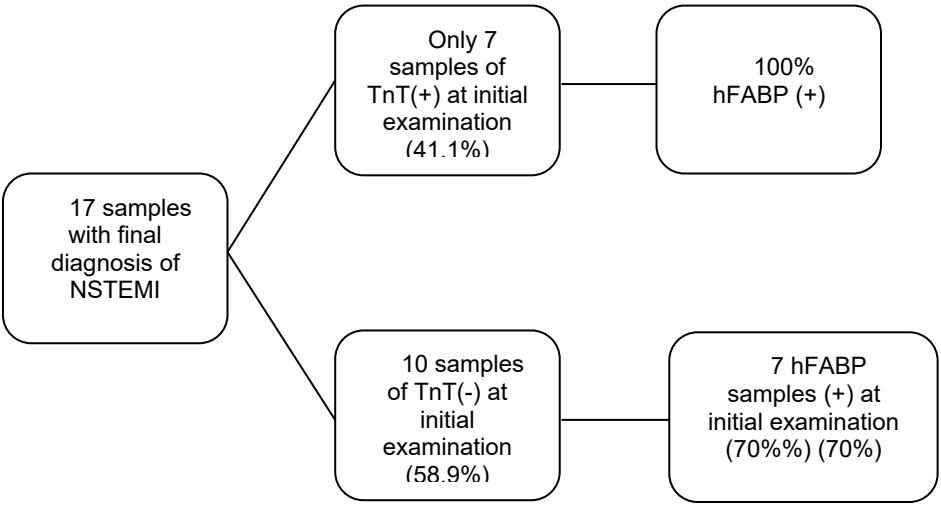

Fig. 3. Diagnostic value of hFABP in NSTEMI patients.

4 Discussion

This study shows that the sensitivity, negative predictive value, and accuracy of hFABP examination in the diagnosis of ≤ 6 hours of AMI onset is quite high and higher than that of the sensitivity, negative predictive value, and accuracy of troponin T assay. These results are the same as the study conducted by Hisamuddin NAR and Suhailan M [13], who also reported that the sensitivity and NPN of hFABP examination were higher than TnT in patients with chest pain onset ≤ 4 hours (50.0% vs 10.0% and 73.6% vs 70.9%) but the specificity and NPP of hFABP examination were lower than TnT (63.6 % vs 100.0 % and 38.4 % vs 100 %). A study conducted by Tong et al. [14], also showed higher sensitivity, specificity, NPP, and NPN, and accuracy of hFABP examination compared to TnT examination in diagnosing AMI in patients with chest pain onset ≤ 6 hours. Nakata et al. [15], also reported that hFABP has greater diagnostic ability compared to other cardiac biomarkers in diagnosing AMI onset ≤ 12 hours.

Heart-type fatty acid-binding protein is a cytoplasmic protein with a low molecular weight (15 kDa) which is abundant in the cytosol of cardiac muscle cells. The low molecular weight and abundant amount causes hFABP to be released quickly into the cytoplasm compared to other cardiac biomarkers in case of ischemia of the cardiac muscle [16]. hFABP levels begin to rise within 30 minutes to 1 hour of ischemic onset, reach a peak in 6-8 hours, and return to normal within 24-36 hours of ischemic onset. Meanwhile, troponin T begins to increase within 3-6 hours and reaches a peak within 14-18 hours after ischemic onset. This condition causes a lower sensitivity to toponin T compared to hFABP in the first hours of ischemic onset [17]. Early detection in circulation in patients with chest pain suspected of ACS provides better diagnostic ability compared to other cardiac biomarkers, such as myoglobin, CKMB, and TnT, especially in patients admitted to hospital at onset ≤ 6 hours from the onset of chest pain symptoms.

Early diagnosis of AMI patients is needed for early treatment. In patients with chest pain with ECG ST elevation, the diagnosis of IMA can be established earlier without having to wait for myocardial infarction biomarkers. However, about 40% of AMI patients are admitted to the hospital with atypical ECG features. In these patients the role of biomarkers is very important. The problem is that it takes about 3-4 hours from the onset of chest pain for biomarker levels (troponin or CKMB) to rise. For this reason, biomarkers are needed that can detect AMI events more quickly. The results of this study indicate that hFABP is quite sensitive in detecting MI in patients with chest pain onset ≤ 6 hours with non-ST elevation EKG and negative troponin T. A study by Alhashemi [18], also showed the same result, where hFABP is very useful for diagnosing IMA in patients with atypical chest pain with non-ST elevation ECG and negative troponin T.

5 Conclusions

The sensitivity, NPN, and accuracy of hFABP examination were higher than troponin T in diagnosing AMI in patients with chest pain onset ≤ 6 hours. In patients

with early onset chest pain with non-ST elevation EKG and negative troponin T, hFABP can be used to predict the incidence of MI. Therefore, it is recommended that patients with early onset chest pain (≤ 6 hours) should be tested for hFABP to help diagnose AMI.

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