

Review Article

Heart-type fatty acid binding protein (H-FABP) as a biomarker for acute myocardial injury and long-term post-ischemic prognosis

Xiao-dong YE¹, Yi HE^{1,2}, Sheng WANG², Gordon T WONG¹, Michael G IRWIN^{1,*}, Zhengyuan XIA^{1,*}

¹Department of Anaesthesiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; ²Guangdong Cardiovascular Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, China

Abstract

Acute myocardial infarction (AMI) is a life-threatening event. Even with timely treatment, acute ischemic myocardial injury and ensuing ischemia reperfusion injury (IRI) can still be difficult issues to tackle. Apart from radiological and other auxiliary examinations, laboratory tests of applicable cardiac biomarkers are also necessary for early diagnosis and close monitoring of this disorder. Heart-type fatty acid binding protein (H-FABP), which mainly exists inside cardiomyocytes, has recently emerged as a potentially promising biomarker for myocardial injury. In this review we discuss the sensitivity and specificity of H-FABP in the assessment of myocardial injury and IRI, especially in the early stage, and its long-term prognostic value in comparison with other commonly used cardiac biomarkers, including myoglobin (Mb), cardiac troponin I (cTnI), creatine kinase MB (CK-MB), C-reactive protein (CRP), glycogen phosphorylase isoenzyme BB (GPBB), and high-sensitivity cardiac troponin T (hs-cTnT). The potential and value of combined application of H-FABP with other biomarkers are also discussed. Finally, the prospect of H-FABP is summarized; several technical issues are discussed to facilitate wider application of H-FABP in clinical practice.

Keywords: acute myocardial infarction; post-ischemic myocardial injury; ischemia reperfusion injury; heart-type fatty acid binding protein; cardiac biomarkers

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Introduction

Coronary artery disease (CAD) is a type of cardiovascular disease that is common worldwide and can lead to severe adverse cardiac events in most cases. Impaired coronary perfusion (angina) is often triggered by exercise or psychological stress, and the symptoms usually last less than half an hour. However, complete occlusion of a coronary artery will lead to permanent damage of the underlying cardiac muscle if not treated promptly (myocardial infarction). These severe adverse cardiac events usually present as chest pain and shortness of breath. Diabetes, hypertension, smoking, hypercholesterolemia, and genetic makeup are all possible risk factors for CAD. Confirmation of diagnosis may require electrocardiography (ECG) and coronary angiography (CAG). Rarely, patients with CAD might have no symptoms at all. However, in many cases of coronary occlusion, patients will develop

arrhythmia and progress to cardiac failure or even sudden death^[1]. Those who manage to survive a myocardial infarction can still suffer from post-ischemic myocardial injury, with their cardiac function seriously compromised. The immediate and most important way to address myocardial infarction is to restore the blood supply to the ischemic heart via percutaneous coronary intervention (PCI) therapy, thrombolysis or coronary artery bypass grafting (CABG). Paradoxically, even timely restoration of coronary blood flow may cause further injury to the ischemic heart, a phenomenon that is termed ischemia reperfusion injury (IRI)^[2]. In 2010, CAD alone was reported to cause more than 7 000 000 deaths globally, even with the advancement of biomedical research and modern technology^[3], representing a great burden on human health and, subsequently, on society. Previously, clinicians have mainly focused on the treatment of CAD with less effort made to efficiently reduce the incidence of relevant complications. Therefore, more attention will need to be paid to the prevention and early treatment of CAD-related complications.

Since it often takes several hours or even days from the presentation of relevant symptoms to the application of CAG in

*To whom correspondence should be addressed.

E-mail zyxia@hku.hk (Zhengyuan XIA);

mgirwin@hku.hk (Michael G IRWIN)

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most patients, auxiliary examination methods, such as ECG, are normally arranged upon patients' visits and can play a vital role in the prediction and even early diagnosis of CAD during this crucial time interval. Additionally, detection of changes in the plasma levels of cardiac biomarkers is routinely used at the early stage of disease onset as it may be difficult to differentiate symptoms from other less important events such as gastroesophageal reflux and muscle strains. In clinical practice, these cardiac biomarkers are helpful for clinicians to make appropriate decisions before the final diagnosis is confirmed. However, as different biomarkers may vary greatly in terms of their respective sensitivity and specificity, it is necessary to continue to search for new types of cardiac biomarkers that can facilitate a faster prediction of immediate and also long-term post-ischemic myocardial injury.

Cardiomyocytes are rich in various proteins and enzymes, including myoglobin (Mb), troponin, creatine kinase (CK), lactic dehydrogenase (LDH), and creatine kinase MB (CK-MB). When cardiomyocytes are damaged, these proteins and enzymes can be released and distributed into the blood flow following cardiomyocyte necrosis and break-down. Hence, the elevation of certain relevant cardiac proteins and enzymes in plasma might indirectly signify myocardial injury and, to some extent, can even reflect its severity.

Currently, cardiac troponin I (cTnI), Mb, and CK-MB are the three biomarkers that are most often used in the hospital to assess the possibility of acute myocardial infarction (AMI) among suspected patients with typical symptoms, such as chest pain. cTnI is a highly specific biomarker for AMI; however, it is not very sensitive in the first hours after AMI. Mb, however, is rather sensitive and is elevated approximately within 3 h after AMI. However, its cardiac specificity is limited, as an injury to the striated muscles in other parts of the human body will also release Mb into blood and raise its plasma concentration. For decades, CK-MB has been considered the most widely accepted biomarker for myocardial injury worldwide. However, despite its popularity, CK-MB is not as sensitive as believed, particularly within 6 h after the onset of AMI. Although the combination of detection and close monitoring of these three markers has proven effective for diagnosing AMI, there is still an urgent need to look for new biomarkers with higher sensitivities and specificities, especially in the very early stage of myocardial injury.

Heart-type fatty acid binding protein (H-FABP) is a type of intra-cardiac protein that plays an essential part in the metabolism of fatty acid (FA) inside cardiomyocytes^[4]. H-FABP was first reported to be a potential indicator for myocardial injury in 1988^[5]. In recent years, there has been increasing interest in the potential role of H-FABP as a biomarker for immediate myocardial injury and even for relatively long-term post-ischemic prognosis. Studies have shown that H-FABP is extraordinarily sensitive in the first hours after myocardial injury^[6] and during reperfusion injury^[7]. The present study reviews the basic characteristics, potential roles, and relevant research studies regarding H-FABP to discuss whether it is suitable to serve as a sensitive and reliable biomarker for acute

myocardial injury and, if possible, for long-term post-ischemic prognosis in comparison with other markers that are routinely used in clinical practice.

Post-ischemic myocardial injury/dysfunction

CAD affects millions of people throughout the world and is widely believed to be the most common cause of mortality worldwide^[8]. As a result of the improvement in modern medicine and increased awareness of public health, there has been a trend of an apparent reduction in both the incidence and mortality of CAD in developed countries over the past decade^[9]. By contrast, the situation in developing countries, unfortunately, is getting worse in that both the prevalence and mortality of CAD are continuously increasing^[10]. Proper management of post-ischemic myocardial injury and relevant complications might help to reduce the incidence of adverse events among patients with CAD.

For patients with atherosclerosis, there is a high chance of AMI and development of post-ischemic myocardial complications. During the pathological process, the endothelium of an atherosclerotic coronary artery can become hardened, making its wall less elastic and thus limiting the volume of blood flow. Additionally, with the deposition of calcium phosphate, cholesterol, fatty acids and formation of foam cells transformed from macrophages, a typical plaque forms. As the plaque continues to grow, the lumen of the coronary artery becomes narrower, reducing the volume of blood flow, leading to myocardial ischemia. At this stage, patients can have angina pectoris and typical chest pain will present in most cases. Taking a rest and/or application of medications, such as nitroglycerin, are normally helpful to relieve symptoms. However, the condition will worsen as the plaque grows larger and the coronary artery lumen becomes extremely narrow. There is a very high chance of AMI when more than 75% of the coronary artery luminal area is blocked. However, AMI is still possible even when the plaque does not block 75% of the coronary artery luminal area as it can become unstable if there is necrosis and a rupture of the intima. Thrombus in the plaque can either cause local occlusion or detach from the original site and then travel as an embolus to cause an occlusion of other smaller segments of coronary arteries. When one or more of the branches of the coronary arteries are occluded, there will only be a tiny amount of or, in severe cases, no blood flow to nourish the corresponding part of the heart. Without enough oxygen and essential nutrients, the regional cardiomyocytes supplied by the occluded coronary artery will immediately suffer from ischemic injury. ATP production and cellular metabolic functions can be severely interrupted. As the ischemia continues, the injury to cardiomyocytes will become irreversible and massive cell death is inevitable, which is what occurs during AMI or a heart attack.

After the diagnosis of AMI is confirmed, PCI or CABG will be scheduled for patients to recanalize the occluded coronary artery. However, restoring blood perfusion to coronary circulation is often followed by IRI, a result of oxidative and inflammatory injuries caused by oxidative stress^[11], which results in

further tissue damage of the infarcted heart. Therefore, attention needs to be paid to protecting patients from further injuries following revascularization. Moreover, patients with CAD and concomitant diabetes mellitus are even more vulnerable to myocardial IRI as they are less or not sensitive to cardioprotective interventions, such as ischemic pre- or post-conditioning, that are otherwise effective for patients without diabetes mellitus^[12-14]. However, the exact mechanism underlying the above phenomenon has yet to be identified. There have been studies suggesting that a reduction in the level of adiponectin may be attributable to the loss of cardio-protection against IRI during hyperglycemia. Our recent study conducted on rats with type I diabetes mellitus revealed that hyperglycemia impaired the Adiponectin/Caveolin-3/STAT3 pathway and thus diminished ischemic post-conditioning protection^[15]. However, there is still much work to be done to comprehensively clarify this issue. Given that scientific research, in an effort to identify an effective treatment for IRI, is still ongoing, the need to seek novel sensitive biomarkers to reflect or even predict the severity of IRI should not be neglected. This review, therefore, will also discuss the potential of H-FABP as a marker to evaluate IRI to facilitate corresponding management.

Commonly used myocardial markers

Mb, cTnI, and CK-MB are the most common biomarkers used to assess myocardial injury in hospitals. Other markers include C-reactive protein (CRP), glycogen phosphorylase isoenzyme BB (GPBB), and high-sensitivity cardiac troponin T (hs-cTnT). The sensitivity, specificity, and prognostic value of these biomarkers are presented and compared in Table 1.

Mb

Mb is a type of protein that is detected inside muscle tissues and is capable of binding oxygen and iron and carrying them during metabolism^[16]. Mb is mainly found in the myocardium and skeletal muscles. Therefore, the presence of Mb in the plasma might indicate a muscle injury. Since Mb has a relatively small molecular weight, it is rapidly released into the circulatory system after muscle damage. The plasma concentration of Mb can be elevated 2–4 h after AMI and can peak approximately 6 h after AMI^[17]. Hence, Mb is regarded as one of the most sensitive biomarkers for AMI, especially at the early stage. However, its specificity can be disappointing in some situations, as Mb exists in all striated muscles. It is difficult to determine whether an increased Mb plasma concen-

tration is the consequence of a myocardial injury or skeletal muscle injury. Elevation of the Mb level can also be seen in patients with impaired kidney function when the kidney fails to filter Mb efficiently^[18]. As a result, an Mb test alone can only be treated as a screening method to rule out AMI. It is advised that Mb should be incorporated with other tests to diagnose AMI. For example, the combination of Mb and carbonic anhydrase III can make Mb a more specific biomarker for AMI even at an early stage^[19]. Mb is also highly sensitive during post-ischemic reperfusion injury; a previous study showed that Mb can be used as an effective marker to identify the patency of a coronary artery following ischemic insult^[20]. Researchers have attempted to use Mb as a prognostic marker for AMI^[21-23]. However, the results were not satisfactory possibly because of the fast clearance of Mb from the plasma.

cTnI

cTnI is a small-sized molecule that exists in the heart muscle. It has a molecular weight of approximately 23.9 kDa. The plasma concentration of cTnI in normal human subjects is rather low or even undetectable. Consequently, cTnI has been the most specific biomarker for AMI during the last two decades. The sensitivity of cTnI is very high, though it is not released into blood as quickly as Mb during myocardial ischemia/reperfusion. Therefore, cTnI has been accepted by clinicians as the best biomarker, and to date, it is even better than the recognized golden biomarker CK-MB for diagnosing AMI. Myocardial injury is highly suspected if the plasma level of cTnI exceeds the upper limit. Irreversible heart muscle cell death is considered if the plasma concentration of cTnI continues to increase. However, the chance of AMI is small if the plasma level of cTnI remains negative for hours.

cTnI, but not other markers, has also been incorporated into new assays to diagnose unstable angina^[24] and identify relevant long-term adverse events^[25]. Additional studies support the prognostic significance of cTnI for patients with acute coronary syndrome (ACS)^[26, 27]. One meta-analysis showed that high-sensitive troponin assays had a fairly good prognostic value for AMI as well^[28]. Benamer *et al*^[29] compared the prognostic significance between cTnI and CRP and found that the levels of plasma cTnI within 24 h after admission could independently forecast a patient's prognosis.

CK-MB

CK-MB is one of the three isoforms of the enzyme creatine

Table 1. Comparisons of several commonly used cardiac biomarkers.

	Mb	cTnI	CK-MB	CRP	GPBB	hs-cTnT	H-FABP
High sensitivity	√	√	-	-	√	√	√
High specificity	-	√	-	-	-	-	√
Good prognostic value	-	√	-	-	-	√	√

Mb: myoglobin; cTnI: cardiac troponin I; CK-MB: creatine kinase MB; CRP: C-reactive protein; GPBB: glycogen phosphorylase isoenzyme BB; hs-cTnT: high-sensitivity cardiac troponin T; H-FABP: heart-type fatty acid binding protein.

kinase (CK). CK is not specific to AMI, as it exists in cerebral, myocardial, and skeletal tissues. In some cases with mild myocardial infarction, CK elevation might not be detected, indicating its lack of satisfactory sensitivity. Therefore, the CK test has been gradually abandoned and replaced by CK-MB because it is more specific in the heart muscle. Actually, CK-MB has already been recognized as the golden marker for AMI for the past two decades. The plasma concentration of CK-MB increases 4–6 h after AMI and reaches the highest level within 24 h. Usually, the CK-MB level will return to a normal range 48–72 h after the onset of AMI. As a biomarker, CK-MB is fast, economical, and efficient for AMI diagnosis and thus has been widely applied in clinical practice globally. Some studies also proved that CK-MB can be used to estimate the infarct size^[30–32] and even the left ventricular ejection fraction^[33]. In addition, CK-MB can also serve as a marker for IRI. Numerous clinical trials have adopted CK-MB as an auxiliary examination for the assessment of reperfusion injury after restoration of coronary circulation^[34, 35]. In addition, CK-MB has been considered to have prognostic significance for post-ischemic mortality and long-term death^[36, 37]. However, Domanski *et al*^[38] showed that troponin T is a better prognostic factor than CK-MB for long-term postoperative mortality after CABG.

However, CK-MB has some drawbacks when utilized as a marker for AMI. The specificity of CK-MB, though much better than that of CK, is still not favorable, as skeletal disorders can cause CK-MB elevation as well. Additionally, the sensitivity of CK-MB is compromised within 6 h after AMI, making it inappropriate as an early predictor. Studies also have demonstrated that CK-MB is a less eligible biomarker than cTnI for the diagnosis of minor myocardial injury^[39, 40]. Yet, CK-MB remains the most popular AMI biomarker despite the fact that new biomarkers are continuously reported.

CRP

It has been gradually acknowledged that the inflammatory response plays a key role in myocardial infarction^[41]. CRP is a common marker for inflammation. It originates from the liver and is triggered by the cytokines that are secreted by adipocytes and macrophages. It is reasonable to correlate CRP to myocardial injury^[42]. Circulating CRP has long been recognized as a promising indicator for adverse coronary events among patients with either stable or unstable angina pectoris^[43]. CRP can also be an excellent prognostic factor for myocardial infarction. Mather *et al*^[44] claimed that the postoperative CRP level 2 days after PCI can serve as the strongest biomarker to predict left ventricular remodeling. Liu *et al*^[45] found that the combination of complementary and high-sensitivity CRP measurements after AMI can efficiently forecast left ventricle dysfunction. While CRP is valuable as a predictor for myocardial injury, consensus and a standardized criterion have yet to be reached for its wide application as a cardiac biomarker in the hospital.

GPBB

As an isoform of glycogen phosphorylase, GPBB has an essen-

tial role in the process of glycogenolysis. GPBB is mainly found in heart and brain tissues and is responsible for providing fuel for energy production during muscle contraction. During myocardial ischemia, GPBB accelerates glycogenolysis for anaerobic glycolysis. Additionally, GPBB can be detached from glycogen and released into the plasma when cell membrane permeability increases following myocardial ischemic insult. GPBB is very sensitive as its plasma concentration usually increases within 1–4 h after AMI, making it comparable to Mb in terms of sensitivity. Previously, large amounts of evidence showed that GPBB could be a promising biomarker for myocardial infarction^[46–48]. However, a group of studies with negative findings have gradually been reported. Mion *et al*^[49] and McCann *et al*^[50] were both surprised to find that the combination of troponin and GPBB did not improve the sensitivity of troponin alone. In 2011, a large-scale clinical trial conducted by Keller *et al*^[51] did not support the diagnostic value of GPBB as an early biomarker for AMI. Yet, GPBB remains a possible prognostic factor for patients with suspected acute coronary syndrome (ACS). Lillpopp *et al*^[52] measured the GPBB levels in patients with chest pain upon admission and found that GPBB is valuable in improving the mid-term prognosis in these patients. Given that increasing evidence has denied the diagnostic value of GPBB for myocardial injury, further research is needed to assess its prognostic value.

hs-cTnT

Troponin T is one of the subtypes of troponins, and cardiac troponin T (cTnT) is a type of heart-specific structural protein that is found inside cardiomyocytes. Similar to cTnI, cTnT is released into plasma when there is a myocardial injury or cardiomyocyte death. With the advancement of technology, the detection of cTnT can be carried out using hypersensitive methods, *ie*, the hs-cTnT assay, to obtain even more sensitive results. The sensitivity of hs-cTnT is excellent as it is elevated and can be detected within 3 h after AMI. Thus, detection of hs-cTnT can help diagnose or exclude AMI at an early stage. In recent years, hs-cTnT has gained popularity in hospitals as a new cardiac biomarker. A multicenter study conducted from 2006 to 2008 confirmed the diagnostic value of hs-cTnT in the early diagnosis of AMI among patients with recent chest pain^[53]. Moreover, hs-cTnT is capable of detecting micro infarcts or minimal necrosis with excellent diagnostic accuracy, *eg*, among patients with non-ST-segment elevation myocardial infarction, which cannot be detected by conventional assays^[54, 55].

Although cTnT is heart tissue-specific, there are a few problems involving the specificity of hs-cTnT. It is reasonable that an increase in the sensitivity over the traditional cTnT assay will likely result in a decrease in its specificity. Thus, there might be greater false positive results in the diagnosis of AMI as the elevation of hs-cTnT is not necessarily relevant to ischemic causes^[56] or even cardiac causes^[57]. Accordingly, an accurate diagnosis of AMI using hs-cTnT would also require comprehensive consideration of a patient's signs, symptoms, ECG, and other laboratory test results. However, the prognostic

value of hs-cTnT is remarkable. Elevation of hs-cTnT among patients with stable or unstable angina is highly correlated to increased long-term mortality^[58]. Reichlin *et al*^[59] performed an international multicenter study from 2006 to 2009 and concluded that elevated hs-cTnT could be used to identify poor prognosis of patients with small AMI. Overall, hs-cTnT might be a favorable option with good cost in the management of AMI^[60].

H-FABP

General information

Fatty acid binding proteins (FABPs) are a group of proteins that are responsible for the transportation of fatty acids and lipophilic materials into or out of cells^[4]. There are several types of tissue-specific FABPs, including liver-type, intestinal-type, heart-type, adipocyte-type, epidermal-type, ileal-type, brain-type, myelin-type, and testis-type FABPs^[4]. Among them, heart-type FABP (H-FABP) is mainly found in the heart and has a molecular weight of 15 kDa. When there is an ischemic injury to the myocardium, H-FABP will rapidly be released into the circulatory system and then be eliminated by the kidney. Consequently, serum H-FABP measurement can, to some extent, reflect myocardial injury. Actually, H-FABP is so sensitive that it has already been utilized clinically as a marker to evaluate sub-clinical ischemia and to predict possible disease progression^[61]. In addition, H-FABP is also apparently correlated to other clinical parameters in AMI patients, *eg*, leukocytosis and a significantly decreased ejection fraction^[62]. These properties of H-FABP might help to understand the pathological process of AMI in a more comprehensive way and hopefully also help to guide the diagnosis as well as treatment. H-FABP is not only a sensitive marker for myocardial injury when it is over-expressed but it has also been shown to promote inflammation, growth and migration of vascular smooth muscle cells, and thus, it possibly plays a role in the pathophysiology of in-stent restenosis^[63]. Therefore, it is reasonable and also valuable to investigate the diagnostic and prognostic potential of H-FABP.

Diagnostic property for AMI

H-FABP is highly sensitive to myocardial ischemic injury as it can be detected as early as 1 h after AMI. In 1992, Kleine *et al*^[64] studied the release of H-FABP after AMI and found that its plasma concentration significantly exceeded the threshold level in less than three hours after AMI. In fact, H-FABP is actually more sensitive than most other cardiac biomarkers. Ishii *et al*^[65] measured the levels of H-FABP and myoglobin within six hours after chest pain and found that H-FABP is much better than myoglobin in regard to both sensitivity and specificity for diagnosing AMI. Furthermore, Ecollan *et al*^[6] tested the levels of H-FABP, CK-MB, Mb, and cTnI among patients with suspected AMI before hospital admission and found that H-FABP possesses significantly superior sensitivity to any of the other three markers. Therefore, the H-FABP test is preferably recommended as the first choice to diagnose or rule out AMI at an early stage, particularly within three hours

after the onset of chest pain.

Additionally, H-FABP is fairly satisfactory in regard to specificity as it is relatively tissue-specific to the heart. A study by Pyati *et al*^[66] revealed that both the sensitivity and specificity of H-FABP are better than those of CK-MB and Mb at 3 h and 3–6 h after a complaint of typical chest pain. Yet, the specificity of H-FABP is not as high as that of the troponin assay^[67]. As a result, Vupputuri *et al*^[68] proposed that a combined application of H-FABP at the early stage and cTnI at the late stage should be employed to achieve a perfect balance between sensitivity and specificity over the whole diagnostic window. Moreover, a patient's conditions can also be influential to the specificity of H-FABP. Garcia-Valdecasas *et al*^[69] reported an unfavorable specificity of H-FABP for AMI, despite its excellent sensitivity and prognostic value. This unfavorable specificity was possibly explained by concomitant renal failure in many patients who were enrolled, disturbing the elimination of H-FABP and thus producing false positive results. Therefore, a combination of H-FABP with other cardiac biomarkers is highly recommended to achieve favorable diagnostic accuracy in clinical practice.

Marker for ischemia reperfusion injury

To effectively remove an occlusion of the coronary artery and re-perfuse the infarcted section of the heart, treatments such as PCI or CABG are normally requested. Yet, the restoration of coronary flow is inevitably followed by IRI and, subsequently, an increased level of cardiac markers, such as H-FABP^[70]. Therefore, H-FABP can also serve as a marker for IRI and indirectly reflects the patency of the coronary artery and restoration of coronary flow.

As a result of its superior sensitivity to other markers, there have been studies that used H-FABP to evaluate the achievement of heart reperfusion after ischemic attack^[71, 72]. In 2000, Hayashida *et al*^[73] compared the plasma concentrations of H-FABP, CK-MB, and troponin T in patients after CABG and concluded that H-FABP is a sensitive early biomarker for IRI. In clinical practice, the studies of Wong *et al*^[74] and Huang *et al*^[7] both included H-FABP as a marker to evaluate IRI in patients undergoing CABG surgery using cardiopulmonary bypass. Huang *et al*^[7] also found H-FABP to be a more sensitive marker than cTnI and CK-MB for sensing post-ischemic myocardial reperfusion injury; thus, they proposed H-FABP to be an early predictor for peri-operative anesthetic cardioprotection against IRI.

Prognostic property

In addition to serving as a marker for AMI and IRI, H-FABP might also have prognostic characteristics. It is not unusual that, even after immediate and proper treatment, patients with AMI are likely to eventually have additional major cardiac events or even death. Since many of the common biomarkers we use do not have satisfactory prognostic value, it is of great importance to explore and employ other new assays to efficiently predict the outcomes of AMI patients. In 2005, Suzuki *et al*^[75] proposed that H-FABP could be a biomarker

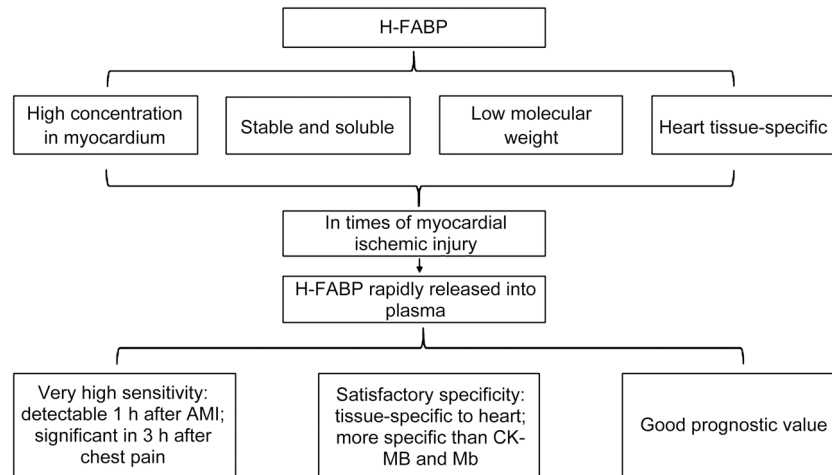


Figure 1. H-FABP as a potential cardiac biomarker.

that can independently predict adverse cardiac events within 30 days in patients with ACS. Then, in 2006, O'Donoghue *et al*^[76] reported a study on a large cohort of 2287 patients and demonstrated that elevated H-FABP in the early hours was related to an increased chance of death and other adverse cardiac events among patients with ACS and that H-FABP alone might provide information for a risk evaluation for clinicians. Additionally, Ishii *et al*^[77] claimed H-FABP to be a potentially independent prognostic factor within 6 months for patients with ACS, even superior to cTnT. Apart from its predictive value on long-term mortality, another prospective observational study also found that H-FABP was capable of identifying high-risk patients with adverse outcomes and that proper attention should be paid to these patients to improve their prognoses^[78]. Furthermore, when used in combination with troponin, an H-FABP measurement could help with prediction of both long-term mortality and the chance for re-infarction in the presence of suspected ACS, even for low- to intermediate-risk subjects^[79]. In addition, it is recommended that checking the H-FABP level only during a hospital stay is insufficient and that continuous follow up is needed. A recent study by Matsumoto *et al*^[80] showed that an H-FABP measurement during the recovery stage of post-AMI patients could predict long-term mortality and the chance of readmission as a result of possible heart failure, even after discharge.

Conclusion

Prevention and early diagnosis are still the main principles in the management of AMI and require specific and sensitive biomarkers for the assessment of a post-ischemic myocardial injury. The present review suggests that H-FABP might be an ideal option based on the currently available evidence. It is highly sensitive and its plasma concentration increases even earlier than that of Mb after myocardial injury. The specificity of H-FABP is also sufficiently satisfactory, though slightly inferior to that of cTnI. As a result of its excellent sensitivity, it can also serve as a good marker for IRI. These properties of

H-FABP could help clinicians to monitor AMI in a timely and close fashion and develop methods to reduce post-ischemic adverse effects. In addition, H-FABP is a potential prognostic indicator for long-term mortality. It should be noted, however, since the diagnostic window of H-FABP is slightly narrow and is eliminated quickly, the combination of H-FABP with other biomarkers, *eg*, H-FABP at the early stage and cTnI at the late stage of AMI is advised to achieve better diagnostic and prognostic significance.

Overall, the future prospect of H-FABP is rather promising (Figure 1). Yet, there are several issues to be addressed before it can be widely applied in hospitals. To promote fast and wide application, it is necessary to develop a sensitive assay to allow fast and convenient as well as economic measurements of H-FABP. In addition, consistent standardization needs to be settled internationally and a consensus should be reached regarding its threshold value as uniform diagnostic criterion. To achieve this, there is still an urgent need for more relevant research studies incorporating clinical trials in multiple centers before H-FABP is recognized as an accurate and reliable marker for immediate and long-term post-ischemic myocardial injury/dysfunction.

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