

Since 1999, work has been carried out with HFABP, many of which have been leading the way for those of us who believed that it was an additional aid in the diagnosis of ACS. Especially in those ACS where the ECG and clinical findings did not provide sufficient information or were discordant factors, despite the fact that later and late, it was seen that we were in the presence of an ACS and we had lost time and therefore, cardiac cells.

In 2005, after excellent work, the diagnostic and prognostic value of cardiac fatty acid binding protein (h-FABP) as an early biochemical marker of myocardial injury was revealed.

These were years in which reviews were constant, the work on providing something more in ACS dubious, confusing, I need field work and research that contributed in favour of (2010 Journal of the American College of Cardiology) that cardiac fatty acid binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome with negative troponin.

In India, in the US, in Europe, all in unison trying to look at troponin T and cardiac fatty acid binding protein (h-FABP) as biomarkers in patients presenting with chest pain.

From India it was contributed that cardiac fatty acid binding protein (h-FABP) as an early diagnostic biomarker in patients with acute chest pain and another study on the role of cardiac fatty acid binding protein in the diagnosis of acute myocardial infarction.

A pilot study from Scandinavia shows that cardiac fatty acid-binding protein is a sensitive biomarker for early detection of AMI in troponin-negative patients.

Also in other stages of coronary artery disease, the prognostic significance of cardiac fatty acid-binding protein in patients with stable coronary artery disease was also contributed.

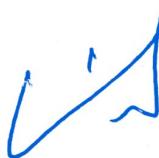
A summary had to be made and then the arguments, benefits and value of the biomarker h-FABP appeared.

Today in cardiology, probably the biggest advances in treatment are in heart failure, so what do we know so far, the cardiac fatty acid binding protein (H-FABP) and its role as a biomarker in heart failure.

And from the latest contributions we have looked at cardiac fatty acid binding protein (HFABP) being related to the severity of heart failure and its known cardiac biomarkers (2021).

Each of the assertions or conclusions has its scientific contribution, its study in patients, even sometimes multicentre, we ourselves are in the development of a new study in several university hospitals to show what we think, what we believe and what we have been able to know, throughout all these years of daily use, which will finally be another tool in the accurate diagnosis of acute coronary syndrome without ST-segment elevation.

In Benidorm, 13 September 2022.



**Dr. Miguel Angel López Aranda**  
**Facultativo Especialista en Cardiología**  
**Jefe de Servicio**  
**Hospital Clínica Benidorm**



# Studies Collection

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K-MARA Healthcare S.L.  
Alicante, Spain

**2005 National Library of Medicine**

Diagnostic and prognostic value of heart- type fatty acid-binding protein (h-FABP), an early biochemical marker of myocardial injury

**2010 Journal of the American College of Cardiology**

Heart-Type Fatty Acid-Binding Protein predicts Long-Term Mortality and Re-infarction in consecutive patients with suspected Acute Coronary Syndrome who are Troponin negative

**2015 India J Clin Biochem**

Troponin T and Heart Type Fatty Acid Binding Protein (h-FABP) as Biomarkers in Patients Presenting with Chest Pain

**2015 Indian Heart Journal 67 (538-542)**

Heart-type fatty acid-binding protein (h-FABP) as an early diagnostic biomarker in patients with acute chest pain

**2016 Department of General Medicine, India**

A Study on the Role of Heart Type Fatty Acid Binding Protein in the Diagnosis of Acute Myocardial Infarction

**2017 Scandinavian Journal of Clinical and Laboratory Investigation**

Heart-type fatty acid binding protein is a sensitive biomarker for early AMI detection in troponin negative patients: a pilot study

**2018 Scientific Report, Published September 26<sup>th</sup>. 2018**

The prognostic significance of heart-type fatty acid binding protein in patients with stable coronary heart disease

**2019 Biognostic Germany**

Arguments, benefits and value of the biomarker h-FABP

- 2019 Journal of Clinical Medicine**  
Heart-Type Fatty Acid-Binding Protein (H-FABP) and Its Role as a Biomarker in Heart Failure: What Do We Know So Far?
- 2020 Annals of Medicine**  
Heart-type fatty acid-binding protein: an overlooked cardiac biomarker
- 2021 Adv Lab Med**  
La proteína de unión a los ácidos grasos cardíaca (HFABP) está relacionada con la gravedad de la insuficiencia cardíaca y sus biomarcadores cardíacos conocidos



## National Library of Medicine

Arch Mal Coeur Vaiss 2005 Dec;98(12):1225-31.

# [Diagnostic and prognostic value of heart-type fatty acid-binding protein (H-FABP), an early biochemical marker of myocardial injury]

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Affiliations expand

- PMID: 16435602

## Abstract

Heart-type fatty acid-binding protein (H-FABP) is a 132 amino acids soluble protein, with general characteristics resembling myoglobin. Because of its low molecular weight (15 kd) and cytoplasmic location, it constitutes a biologic marker readily released into the circulation after myocardial injury. Despite the development of various immunoassays to measure H-FABP, few are currently easy to perform, quantitative and applicable in emergency. Most studies have shown the diagnostic sensitivity of H-FABP (i.e. its ability to detect the presence of a myocardial infarction) to be high, above that of myoglobin in patients presenting within 3 to 6 h of after the onset of chest pain. This superiority is attributable to an earlier and more rapid rise in H-FABP than in myoglobin. After thrombolysis, the serum concentrations of H-FABP peak at approximately 4 h after the onset of chest pain, and return to normal values within 24 h. Because of this rapid return of its blood concentration to baseline, H-FABP can contribute to an early biologic diagnosis of post-thrombolysis reperfusion and re-infarction. In absence of renal insufficiency, H-FABP also provides a reliable estimate of infarct size associated with ST segment elevation. When myocardial injury occurs after cardiac surgery, the second peak in H-FABP concentration precedes that of myoglobin, CK-MB or troponins. In addition, H-FABP peaks earlier and is more sensitive than troponins in the detection of subtle myocardial injury in patients presenting with acute coronary syndrome without ST segment elevation, and in patients with severe heart failure, thus offering early prognostic information. Limitations of H-FABP include a limited cardio-specificity, a narrow diagnostic window (20 to 30 h), and a nearly exclusive renal elimination.

# Heart-Type Fatty Acid-Binding Protein Predicts Long-Term Mortality and Re-Infarction in Consecutive Patients With Suspected Acute Coronary Syndrome Who Are Troponin-Negative

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## Objectives

The purpose of this study was to establish the prognostic value of measuring heart fatty acid-binding protein (H-FABP) in patients with suspected acute coronary syndrome (ACS) (in particular, low- to intermediate-risk patients), in addition to troponin measured with the latest third-generation troponin assay.

## Background

We have previously shown that H-FABP is a useful prognostic marker in patients with proven ACS.

## Methods

Patients ( $n = 1,080$ ) consecutively admitted to the hospital with suspected ACS were recruited over 46 weeks. Siemens Advia Ultra-TnI (Siemens Healthcare Diagnostics, Newbury, United Kingdom) and Randox Evidence H-FABP (Randox Laboratories, Ltd., Co., Antrim, United Kingdom) were analyzed on samples collected 12 to 24 h from symptom onset. After exclusion of patients with ST-segment elevation and new left bundle branch block, 955 patients were included in the analysis.

## Results

The primary outcome measure of death or readmission with myocardial infarction after a minimum follow-up period of 12 months (median 18 months) occurred in 96 of 955 patients (10.1%). The H-FABP concentration was an independent predictor of death or myocardial infarction, after multivariate adjustment. Patients with H-FABP concentrations  $>6.48 \mu\text{g/l}$  had significantly increased risk of adverse events (adjusted hazard ratio: 2.62, 95% confidence interval: 1.30 to 5.28,  $p = 0.007$ ). Among troponin-negative patients (which constituted 79.2% of the cohort), the aforementioned cutoff of  $6.48 \mu\text{g/l}$  identified patients at very high risk for adverse outcomes independent of patient age and serum creatinine.

## Conclusions

We have demonstrated that the prognostic value of elevated H-FABP is additive to troponin in low- and intermediate-risk patients with suspected ACS. Other studies suggest that our observations reflect the value of H-FABP as a marker of myocardial ischemia, even in the absence of frank necrosis. (J Am Coll Cardiol 2010; 55:2590–8) © 2010 by the American College of Cardiology Foundation

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight cytoplasmic protein that is involved in the intracellular uptake and buffering of free fatty acids in the myocardium (1). We have recently demonstrated that

H-FABP predicts long-term mortality in a study of 1,448 patients with acute coronary syndrome (ACS) and that this prediction was independent of the GRACE (Global Registry of Acute Coronary Events) clinical risk factors, troponin and high-sensitivity C-reactive protein (2). In particular, H-FABP was able to identify those troponin-negative patients with unstable angina who were at high risk of subsequent death. This observation has been independently supported by O'Donoghue et al. (3) in their study of 2,287 ACS patients recruited in the Thrombolysis In Myocardial Infarction-16 trial. However, both these studies were performed on selected patients with independently confirmed ACS. Therefore, they offer predictive information on mortality for patients with ACS but cannot be used to provide diagnostic

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information, because they did not include consecutive series with chest pain; there were not significant numbers of either “troponin-negative” or low- to intermediate-risk patients (4). This group of apparently low-risk patients is likely to benefit the most from accurate risk stratification.

Over the past few years, troponin assays have improved, and newer assays can now achieve the analytical performance spelled out in the Joint European Society of Cardiology/American College of Cardiology consensus document on redefining myocardial infarction (MI) published in 2000—which recommended a coefficient of variation (CV) of <10% at the 99th percentile value of a reference healthy population (5). There is emerging evidence that these improvements increase the early diagnostic and prognostic value of the newer troponin assays (6–8). This raises the question of whether there is still additional value in measuring novel markers such as H-FABP in conjunction with the newer troponin assays (9). To address this, we designed and conducted the FAB (Heart-Type Fatty Acid Binding Protein in Suspected ACS) study, which recruited a consecutive series of patients who presented to hospital with suspected ACS. Our primary aim was the evaluation of the complementary value of H-FABP, particularly for those patients found to be negative for troponin measured with a third-generation troponin assay (Advia Centaur TnI-Ultra, Siemens Healthcare Diagnostics, Newbury, United Kingdom).

## Methods

**Study design and patient selection.** The study was a prospective observational study of patients with suspected ACS presenting consecutively to a large teaching hospital in Leeds, United Kingdom. All individuals ages 18 years or above with chest pain of possible or definite cardiac etiology were deemed eligible for recruitment, irrespective of electrocardiographic (ECG) changes. Individuals presenting without chest pain but with other symptoms suggestive of ACS (dyspnea, diaphoresis, back pain, and so forth) were also included, if considered to be compatible with an atypical presentation of ACS by the assessing physician in the emergency department. We excluded patients: 1) who were unwilling or unable to provide informed consent; 2) from whom precisely timed additional blood samples could not be obtained; and 3) who were admitted with an identified non-cardiac cause of chest pain on presentation (such as pneumonia or pulmonary embolism). When in doubt, the final judgment regarding appropriateness of inclusion into the study was made by the research team (2 specialist cardiology nurses and 1 cardiology research physician) at the time of obtaining written consent.

Between May 15, 2006, and April 1, 2007, we enrolled 1,080 consenting patients with suspected ACS, who all provided informed consent for participation and long-term follow-up. Consent was obtained at the earliest opportunity by the research team together with support from doctors

and nursing staff working in the emergency department, as specified in the study protocol. All study subjects were managed in accordance with existing patient care pathways in the hospital, which require all patients with suspected ACS to be admitted either under the care of a cardiologist (if the patient was deemed intermediate or high clinical risk) or in the Clinical Decisions Unit run by the emergency department (if the patient was deemed low-risk) for a period of observation. All individuals enrolled into the study had additional serum and plasma samples taken for the purpose of research at the same time as the clinical blood sample taken for the “routine” troponin testing—at least 12 h from symptom onset. Only the “routine” troponin test sample was analyzed in real time, and the result was made available to the attending physician for further clinical management. Consequently, participation in the study did not influence the routine care and immediate/long-term management. Patients recruited into the study also had an earlier serum sample collected at the time of first contact with the emergency department whenever logistically possible. All additional research samples collected were centrifuged and stored in a -70°C freezer within 4 h of venipuncture and later analyzed as a single batch.

Most research blood samples collected were timed to coincide with “routine” venepuncture, carried out by clinical and support staff, to ensure little additional inconvenience to the patients. The study design was intentionally pragmatic, so as to be readily generalizable to other patients with suspected ACS as well as to maximize the chances of voluntary enrolment into the study to ensure that the final cohort was truly representative of unselected patients with suspected ACS. Demographic and relevant clinical data were collected at the time of consent from patient medical records and patient interview.

All patients were followed up for the occurrence or death and/or MI over a minimum period of 12 months. The date of censorship of follow-up data was April 1, 2008 (median follow-up 18 months). Survival status was obtained through the U.K. Office of National Statistics. We have ensured no loss to follow-up on mortality data from the Office for National Statistics by obtaining data from at least 4 months after the date of censorship to allow for lag time from death to documentation of death. We set out to obtain data on re-admission to hospital with MI from 2 sources—directly from the patients via patient follow-up questionnaires and from the hospital electronic records system. The first methodology yielded responses from only 68% of patients, with many patients expressing ambiguity about the diagnosis of

## Abbreviations and Acronyms

**ACS** = acute coronary syndrome

**CI** = confidence interval

**CV** = coefficient of variation

**ECG** = electrocardiogram

**H-FABP** = heart-type fatty acid-binding protein

**HR** = hazard ratio

**MI** = myocardial infarction

**TnI** = troponin I

MI. By contrast, the information obtained from the hospital electronic records system was robust and reproducible. This was successfully validated on a random sample of patients with patient hospital records and patient follow-up questionnaires. Therefore, we have used this methodology for identification of adverse events of readmission with MI in all our analyses. Because our hospital is the sole provider of emergency care for patients with chest pain in the city of Leeds and the sole provider of primary angioplasty for the entire West Yorkshire region, we expect to have identified the vast majority of recurrent events. A small number of silent events and any occurring outside the West Yorkshire region might have been missed. This would not be expected to produce any bias to our results.

**Laboratory analyses.** Troponin was measured with the Advia Centaur system (Siemens Healthcare Diagnostics). The assay for measuring troponin in routine clinical practice at our recruiting hospital was upgraded partway through the study (September 12, 2006), from Advia Troponin I to Advia TnI-Ultra. However, the troponin value used in routine clinical practice for classifying patients as having had an acute MI was effectively unchanged throughout the study period. For the period when Advia Troponin I was used, the cutoff value was set at  $0.18 \mu\text{g/l}$ , which represented the lowest concentration at which the CV was 10%. When the Advia TnI-Ultra was used, the cutoff value used was  $0.14 \mu\text{g/l}$ , which corresponded to  $0.18 \mu\text{g/l}$  for the Advia Troponin I assay (in-house evaluation). For the purpose of this study and to ensure that all study patients were categorized in accordance with the new universal definition of MI (10), all stored serum samples were analyzed as a single batch at the end of the study, with the highly sensitive Advia TnI-Ultra assay. We determined the cutoff value corresponding to the 99th percentile value of healthy adults for this assay as  $0.05 \mu\text{g/l}$  locally (with a reference population of 299 healthy adults) and have used this throughout this report. We also observed that the single batch analysis showed considerable precision with an intra-assay CV of 10% at a concentration  $<0.01 \mu\text{g/l}$  for Advia TnI-Ultra.

The H-FABP was measured with the Biochip array technology on the fully automated Evidence system (Randox Laboratories, Ltd., Co., Antrim, United Kingdom) with the Cardiac Biochip. This biochip uses a high-precision, chemiluminescent immunometric assay for measuring H-FABP with 2 mouse monoclonal antibodies. We assessed the inter-assay CV to be 5% at a concentration of  $5.8 \mu\text{g/l}$  (99th percentile values for subjects with estimated glomerular filtration rate  $>60 \text{ ml/min}$ ) (11).

**Statistical analyses.** Data are presented as mean  $\pm$  SD unless otherwise stated, and all statistical analyses were performed with SPSS software (version 16, SPSS, Inc., Chicago, Illinois). Groups of patients were compared with the chi-square test for categorical variables and analysis of variance for continuous variables. Event-free survival curves

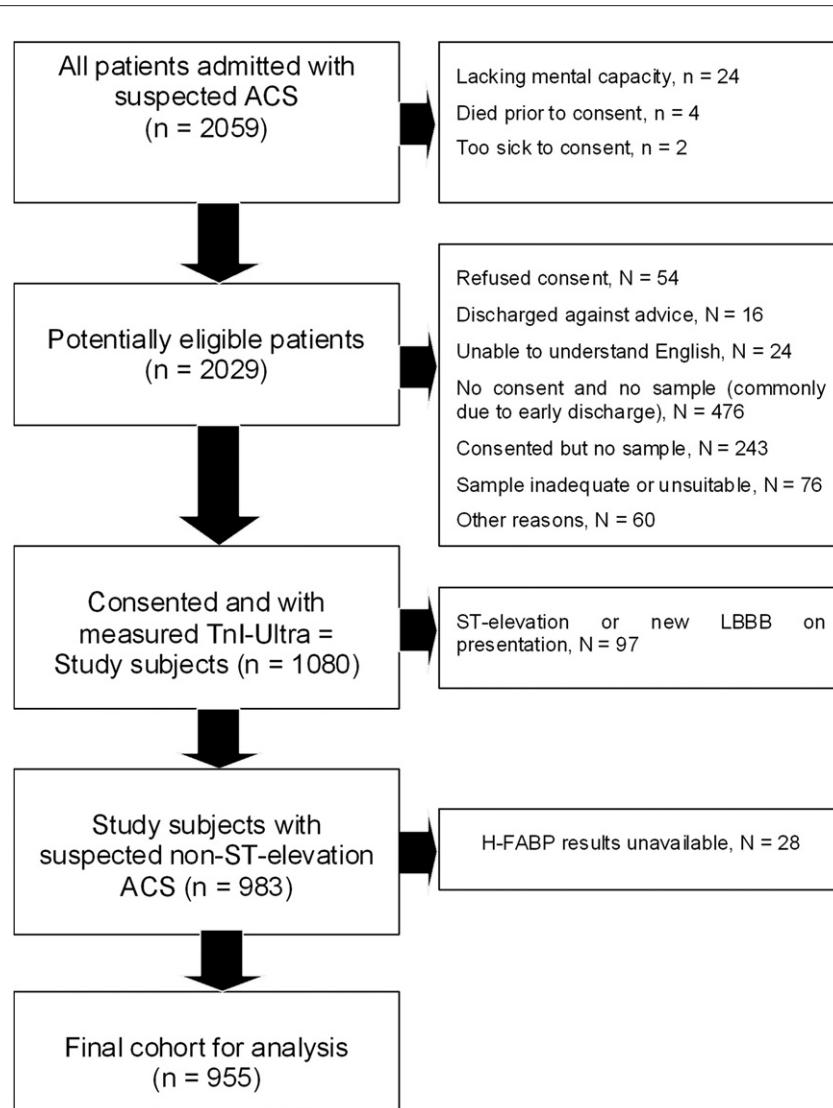
were generated as univariable Kaplan-Meier estimates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by constructing first a univariable and subsequently a multivariable Cox proportional hazards regression model, with death or MI as the dependent variable. For all tests,  $p \leq 0.05$  was considered to be statistically significant.

## Results

**Cohort description and long-term outcomes.** The FAB study identified 1,080 patients admitted to hospital with suspected ACS, all of whom had troponin I (TnI) measured  $>12 \text{ h}$  from symptom onset. Approximately one-half of all individuals admitted with suspected ACS during the recruitment period were included in the study. Figure 1 shows the enrolment of patients into the study. We excluded 97 patients presenting with ST-segment elevation or new left bundle branch block on their ECG and 28 patients in whom H-FABP results were unavailable. The remaining 955 patients were included in the analyses. The mean age of patients included was  $60 \pm 15$  years; 577 were male (60.5%) and 378 were female (39.5%). Advia TnI-Ultra (Siemens Healthcare Diagnostics) had a non-Gaussian distribution with a median concentration of  $0.02 \mu\text{g/l}$  (interquartile range  $0.01$  to  $0.04 \mu\text{g/l}$ ). We classified 199 of 955 (20.8%) patients as having non-ST-segment elevation MI, with Advia TnI-Ultra  $\geq 0.05 \mu\text{g/l}$  (as per the Universal definition of MI). Heart-type fatty acid-binding protein was measured in all 955 patients. We observed a non-Gaussian distribution, with a median concentration of  $2.42 \mu\text{g/l}$  (interquartile range  $1.57$  to  $3.95 \mu\text{g/l}$ ). Table 1 provides a summary of the baseline characteristics across the cohort and further stratified according to H-FABP concentration.

As of April 1, 2008 (median follow-up 18 months), 59 of 955 (6.2%) had died, and the primary outcome measure of death or readmission with MI had occurred in 96 of 955 (10.1%). Table 2 shows the occurrence of death and death or MI—hereafter referred to as “events”—across the study cohort, which has been split into 4 groups on the basis of an equal number of “events.” There is a gradient of increasing risk with increasing concentrations of troponin across the 4 groups. It is also notable that the frequency of inpatient angiography and revascularization in Groups 1 and 2 (in whom all patients were deemed troponin “negative”) is significantly lower than in Groups 3 and 4 (where the vast majority of patients were deemed troponin “positive”). In contrast, the event rate observed increased progressively across all groups.

**Prognostic value of H-FABP across the entire cohort.** Table 3 shows the occurrence of “events” (death or MI) across the cohort stratified by H-FABP results. For this analysis, the entire cohort was split into 4 groups on the basis of equal number of events as follows: Group 1: H-FABP  $<3.26 \mu\text{g/l}$ , Group 2:  $3.27$  to  $6.48 \mu\text{g/l}$ , Group 3:  $6.49$  to  $12.77 \mu\text{g/l}$ , Group 4:  $>12.77 \mu\text{g/l}$ . Patients were



**Figure 1 Enrollment of Patients Into the Study**

Flowchart shows patient enrolment into the study. TnI-Ultra (Siemens Healthcare Diagnostics, Newbury, United Kingdom). ACS = acute coronary syndrome; H-FABP = heart-type fatty acid-binding protein; LBBB = left bundle branch block.

further classified as MI (troponin-positive) or Not MI (troponin-negative) in accordance with the new Universal Definition of MI (10), with the cutoff value of troponin corresponding to the 99th percentile value for healthy adults (i.e., 0.05 µg/l). There is a gradient of increasing risk across increasing concentrations of H-FABP ( $p < 0.001$ ), irrespective of the associated troponin result. Unadjusted HRs for patients in Groups 3 and 4 according to H-FABP concentration (as shown in Table 4) were 15.67 (95% CI: 8.16 to 30.07) and 20.37 (95% CI: 10.38 to 40.00), respectively (both  $p < 0.001$ ), compared with Group 1. Figure 2 shows the corresponding Kaplan-Meier event-free survival curves for the 4 groups according to H-FABP concentration. Table 4 summarizes the findings of the univariate analyses that were performed to assess the mag-

nitude of risk (death or MI at median follow-up of 18 months) associated with various baseline risk factors that were statistically significant across the 4 groups of H-FABP (Table 1). All factors that were significantly associated with risk on univariate analysis were then included in a Cox proportional hazards regression model, and the results of this multivariable analysis are shown in Table 4. The results show that age, previous MI, admission heart rate, and H-FABP concentration remained statistically significant as independent predictors of long-term risk. Patients with H-FABP concentrations in Group 3 (6.49 to 12.77 µg/l) had a significantly increased risk of adverse events with an adjusted HR of 2.62 (95% CI: 1.30 to 5.28,  $p = 0.007$ ), with Group 4 ( $>12.77 \mu\text{g/l}$ ) showing a statistically nonsignificant increase in risk with an adjusted HR of 1.54 (95%

**Table 1** Baseline Characteristics According to H-FABP Groups by Equal Number of Events

	Entire Cohort (Events = 96 of n = 955)	H-FABP Group 1 ≤3.26 µg/l (Events = 24 of n = 635)	H-FABP Group 2 3.27–6.48 µg/l (Events = 24 of n = 203)	H-FABP Group 3 6.49–12.77 µg/l (Events = 24 of n = 63)	H-FABP Group 4 >12.78 µg/l (Events = 24 of n = 54)	p Value
Age, yrs (SD)	60.01 (15.00)	55.44 (13.99)	67.37 (12.22)	72.03 (11.26)	71.93 (14.71)	<0.001
Male sex	60.5%	59.9%	58.6%	68.3%	64.8%	0.50 (NS)
Diabetes	15.1%	11.3%	23.3%	22.6%	19.6%	<0.001
Smoking	24.4%	25.8%	20.2%	21.7%	26.9%	0.40 (NS)
Hypertension	61.2%	40.7%	67.0%	71.0%	61.2%	<0.001
Family history of CAD	55.0%	57.4%	51.5%	42.0%	53.2%	0.13 (NS)
Previous MI	30.5%	22.4%	40.3%	65.1%	47.2%	<0.001
Prior PCI/CABG	23.3%	19.8%	30.7%	33.9%	24.5%	0.003
Previous heart failure	5.1%	2.2%	8.1%	10.9%	23.4%	<0.001
ST-segment depression on ECG	10.6%	4.9%	15.3%	23.8%	44.4%	<0.001
Creatinine, mg/dl (SD)	1.14 (0.30)	1.06 (0.16)	1.22 (0.27)	1.36 (0.30)	1.54 (0.71)	<0.001
Systolic BP, mm Hg (SD)	138.01 (25.41)	136.29 (22.67)	140.98 (27.47)	133.92 (29.13)	152.45 (36.89)	<0.001
Heart rate, beats/min (SD)	77.59 (20.39)	75.05 (17.15)	80.98 (23.47)	82.63 (29.05)	88.74 (24.49)	<0.001
Troponin-negative <0.05 µg/l	79.2%	90.2%	72.9%	50.8%	5.6%	<0.001

BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; H-FABP = heart-fatty acid-binding protein; MI = myocardial infarction; PCI = percutaneous coronary intervention; Q = quartile.

CI: 0.55 to 4.32, p = 0.41). Analyses with receiver-operator curves comparing the value of H-FABP and TnI in predicting long-term adverse events showed H-FABP to be comparable to TnI (area under the curve for H-FABP = 0.79 [95% CI: 0.74 to 0.84] vs. TnI = 0.77 [95% CI: 0.72 to 0.82]), as shown in Figure 3.

**Prognostic value of H-FABP in the TnI-negative subgroup.** In the troponin-negative subgroup (n = 756), there were 40 major adverse events (death or MI) during the follow-up period. Table 3 shows the event rate across each of the 4 groups on the basis of H-FABP concentrations as described in the earlier section. Table 5 shows the unadjusted HRs for troponin-negative patients, after stratifying patients into the same 4 groups. This shows increasing risk in Groups 2, 3, and 4 as compared with Group 1 with a very significantly increased event rate in patients with H-FABP concentrations above 6.48 µg/l (Groups 3 and 4)—unadjusted HR in Group 3: 11.20 (95% CI: 4.95 to 25.36), p < 0.001. Table 5 shows the adjusted HRs after adjustment for age and serum creatinine in a Cox proportional hazards regression model. This confirms the additional prognostic value of H-FABP >6.48 µg/l (adjusted HR: 3.12, 95% CI: 1.11 to 8.76, p = 0.03), independent of age and serum creatinine.

## Discussion

Despite enormous research interest in cardiac biomarkers in recent years, very few have established themselves unequivocally in routine clinical practice. Cardiac troponin remains the cornerstone in the risk stratification of patients with suspected ACS. One of the important criteria for a biomarker is to be able to inform clinical decision-making and thus influence patient management (12). Heart-type fatty acid-binding protein has emerged as an independent prognostic marker for patients with ACS in at least 2 large studies (2,3). The FAB study was specifically designed to complement our earlier study on H-FABP (2) and extend the applicability of the results to contemporary clinical practice by including low-risk subjects. Our study population (excluding those presenting with ST-segment elevation or new left bundle branch block) included 79.2% of subjects with TnI below the 99th percentile, which is consistent with several routine laboratory audits. In this first report resulting from the FAB study, we have confirmed our previous finding for patients with proven ACS—that H-FABP identifies high-risk patients who are troponin-negative.

Since the publication of the New Definition of MI in 2000 (5), there have been few studies reporting long-term major adverse outcomes (death, MI) for a large consecutive

**Table 2** Management and Long-Term Outcomes on the Basis of Troponin Results

	Entire Cohort (n = 955)	TnI Group 1 0.00–0.02 µg/l (Events = 24 of n = 641)	TnI Group 2 0.03–0.08 µg/l (Events = 24 of n = 146)	TnI Group 3 0.09–3.04 µg/l (Events = 24 of n = 99)	TnI Group 4 >3.04 µg/l (Events = 24 of n = 69)	p Value
Inpatient angiogram	15.4% (147)	6.1% (39)	8.2% (12)	49.5% (49)	68.1% (47)	<0.001
Inpatient PCI/CABG	8.1% (77)	1.4% (9)	2.1% (3)	33.3% (33)	46.4% (32)	<0.001
Death	6.2% (59)	2.7% (17)	9.6% (14)	12.1% (12)	23.2% (16)	<0.001
Death or MI	10.1% (96)	3.7% (24)	16.4% (24)	24.2% (24)	34.8% (24)	<0.001

TnI = Troponin I; other abbreviations as in Table 1.

**Table 3** Number of Major Adverse Events Across the 4 Subgroups on the Basis of H-FABP Concentrations and Stratified by Troponin Results

H-FABP Concentration	"Not MI" According to Universal Definition (Troponin <0.05 µg/l)	"MI" According to Universal Definition (Troponin ≥0.05 µg/l)	Total
Group 1 = 0.15–3.26 µg/l (events = 24 of n = 635)	16/573 (2.8%)	8/62 (12.9%)	24/635 (3.8%)
Group 2 = 3.27–6.48 µg/l (events = 24 of n = 203)	14/148 (9.5%)	10/55 (18.2%)	24/203 (11.8%)
Group 3 = 6.49–12.77 µg/l (events = 24 of n = 63)	9/32 (28.1%)	15/31 (48.4%)	24/63 (38.1%)
Group 4 = 12.78–151.00 µg/l (events = 24 of n = 54)	1/3 (33.3%)	23/51 (45.1%)	24/54 (44.4%)
Entire cohort (N = 955)	40/756 (5.3%)	56/199 (28.1%)	96/955 (10.1%)
p value	<0.001	<0.001	<0.001

Major adverse events are death or MI after a median follow-up period of 18 months.

Abbreviations as in Table 2.

population of patients presenting with chest pain/suspected ACS (13–15). In keeping with these published studies, the majority of our subjects were at low-to-intermediate risk.

**Table 4** HRs for Death or MI After Median Follow-Up Period of 18 Months

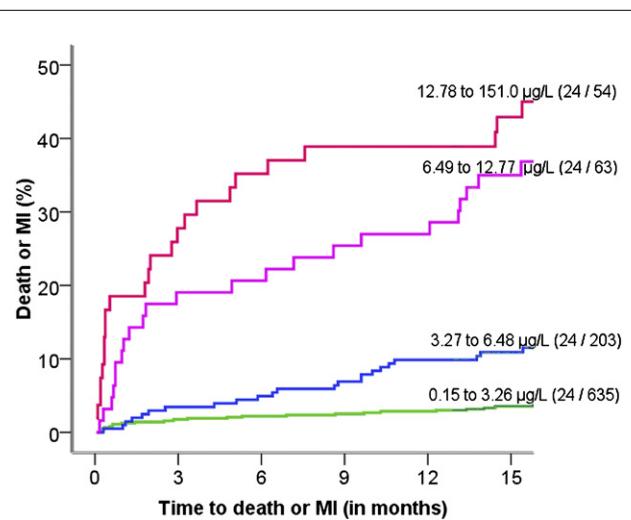
Univariate*	HR (95% CI)	p Value
Age	1.11 (1.08–1.12)	<0.001
Diabetes	2.43 (1.48–3.99)	<0.001
Hypertension	1.95 (1.25–3.05)	0.003
Previous PCI/CABG	1.64 (1.03–2.61)	0.043
Previous heart failure	5.62 (2.89–10.96)	<0.001
Previous MI	4.60 (2.94–7.18)	<0.001
Heart rate	1.024 (1.015–1.033)	<0.001
Systolic BP	1.005 (0.97–1.014)	0.21
ST-segment depression on ECG	6.48 (3.98–10.55)	<0.001
Creatinine	1.025 (1.018–1.033)	<0.001
TnI 0.00–0.02 µg/l	1.00	<0.001
TnI 0.03–0.08 µg/l	5.06 (2.78–9.20)	<0.001
TnI 0.09–3.04 µg/l	8.22 (4.55–15.2)	<0.001
TnI >3.04 µg/l	13.71 (7.22–26.05)	<0.001
H-FABP 0.15–3.26 µg/l	1.00	<0.001
H-FABP 3.27–6.48 µg/l	3.41 (1.89–6.16)	<0.001
H-FABP 6.49–12.77 µg/l	15.67 (8.16–30.07)	<0.001
H-FABP 12.78–151.0 µg/l	20.37 (10.38–40.00)	<0.001
Multivariable†		
Age	1.06 (1.03–1.08)	<0.001
Diabetes	1.67 (0.97–2.87)	0.062
Hypertension	1.06 (0.65–1.73)	0.81
Prior heart failure	1.29 (0.65–2.56)	0.47
Prior MI	1.79 (1.08–2.98)	0.025
Heart rate	1.01 (1.00–1.02)	0.004
ST-segment depression on ECG	1.73 (0.98–3.05)	0.59
Creatinine	1.00 (0.99–1.01)	0.48
TnI 0.00–0.02 µg/l	1.00	0.10
TnI 0.03–0.08 µg/l	2.15 (1.11–4.17)	0.024
TnI 0.09–3.04 µg/l	2.09 (1.01–4.36)	0.048
TnI >3.04 µg/l	2.41 (0.95–6.09)	0.063
H-FABP 0.15–3.26 µg/l	1.00	0.003
H-FABP 3.27–6.48 µg/l	0.78 (0.39–1.55)	0.48
H-FABP 6.49–12.77 µg/l	2.62 (1.30–5.28)	0.007
H-FABP 12.78–151.0 µg/l	1.54 (0.55–4.32)	0.41

\*Unadjusted univariate analysis; †multivariate analysis including all factors noted to be significant on univariate analysis (except previous PCI/CABG in view of borderline significance only on univariate analysis).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

Consequently, we note significantly lower occurrence of death and MI compared with previously published studies on H-FABP that largely included high-risk ACS patients. The event rate in our study was slightly lower than the consecutive chest pain population studies mentioned earlier. This is consistent with global improvement in care of patients with ACS secondary to the increasing use of evidence-based pharmacological therapy (aspirin, clopidogrel, statin, beta-blocker, ACE inhibitor) and coronary intervention.

Recently, McCann et al. (16) reported on the prognostic value of H-FABP among other markers in 664 patients presenting to coronary care unit with ischemic-type chest pain recruited over 3 years. The authors showed that H-FABP and N-terminal pro-B-type natriuretic peptide had independent prognostic value in addition to troponin. Our study confirms the long-term prognostic value of H-FABP demonstrated in this and earlier studies (2,3) in a

**Figure 2** Kaplan Meier Event-Free Survival Curves for Death or MI in the 4 Groups of Patients on the Basis of H-FABP Concentrations

Each curve represents a subgroup of patients defined by the measured concentration of heart-type fatty acid-binding protein (H-FABP). Group 1: H-FABP <3.26 µg/l, Group 2: 3.27 to 6.48 µg/l, Group 3: 6.49 to 12.77 µg/l, Group 4: >12.77 µg/l. For hazard ratios for each of the groups, see Table 4. MI = myocardial infarction.

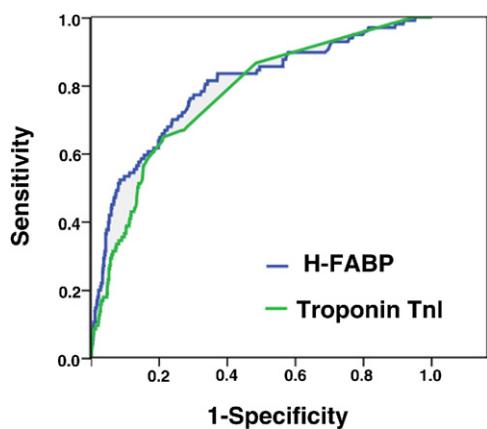


Figure 3

**Receiver-Operator Curves for H-FABP and TnI-Ultra in the Prediction of Death or MI**

Receiver-operator curves for H-FABP and troponin I (TnI) in prediction of death or MI after median of 18 months follow-up. Area under the curve for H-FABP = 0.79 (95% confidence interval 0.74 to 0.84). Area under the curve for TnI = 0.77 (95% confidence interval: 0.72 to 0.82). Abbreviations as in Figures 1 and 2.

larger and unselected consecutive cohort of suspected ACS patients. We have shown that the risk of death or recurrent MI increases with increasing concentrations of H-FABP with a significant increase in patients with H-FABP  $>6.48 \mu\text{g/l}$ , and this is independent of other established clinical risk factors, including troponin. One of the particular strengths of studying an unselected cohort of consecutive patients with suspected ACS (as in our study) is that the results can be extrapolated more readily to contemporary clinical practice. Therefore, we believe that this takes us 1 step closer toward establishing the clinical utility of routine measurement of H-FABP in suspected ACS.

The ideal cutoff value for defining troponin positivity in suspected ACS has been long identified as the 99th percentile value in a population of healthy adults, and this has been reinforced in the more recently published Universal Definition of Myocardial Infarction (10). However, the fact that no commercially available assays were able to achieve the standard of a CV  $<10\%$  at the 99th percentile value until recently has remained a major limitation (17). Therefore, it was likely that before 2008 some patients were misclassified as low-risk, thus overestimating the magnitude of benefit of biomarkers studied in conjunction with troponin. In this study, we measured troponin with the ultra-sensitive TnI-Ultra (Siemens Healthcare Diagnostics) assay, a third-generation troponin assay that satisfies the requirements stated in the Universal Definition of MI (10). It is notable that the independent prognostic value of H-FABP demonstrated in patients with suspected ACS is not negated by the use of the newer ultra-sensitive troponin assays.

We have demonstrated, in particular, that the long-term prognostic value of H-FABP in troponin-negative patients is independent of age and serum creatinine, both of which

have been shown to influence H-FABP concentrations in apparently healthy subjects (11). Our study suggests that troponin-negative patients with H-FABP  $>6.48 \mu\text{g/l}$  represent a very-high-risk group of patients, and we suggest that further investigations such as coronary angiography and appropriate pharmacotherapy are warranted in this small subgroup of patients (35 of 756, 4.6% of all troponin-negative patients in our study).

In a recent publication by our group, we have defined the 99th percentile values for H-FABP measured with 2 commercially available assays in a population of primary and secondary care outpatients (11). The 99th percentile values for subjects with estimated glomerular filtration rate  $>60 \text{ ml/min}$  for the Evidence Investigator H-FABP assay used in this study were 5.3 and 5.8  $\mu\text{g/l}$  in female and male subjects, respectively. In our present study, with this cutoff value to define patients as “elevated H-FABP,” these patients had significantly increased event rate. The unadjusted HRs for death or MI for those with “elevated H-FABP” as defined by this cut-off value were 3.70 (95% CI: 1.82 to 7.56,  $p < 0.0001$ ) in troponin-positive patients and 6.57 (95% CI: 3.05 to 14.11,  $p < 0.0001$ ) among troponin-negative patients.

We acknowledge a few limitations of this study. It must be noted that 53.2% of eligible patients admitted during the period of recruitment were enrolled into the main study. This was largely because, although patients with suspected ACS present 24 h/day and 7 days/week, participation in a study of this nature requires informed consent and precisely timed sample collection within a few hours of hospital admission—making the study logically quite challenging. The exclusion of patients from the study (Fig. 1) was random, and we believe that this was unlikely to introduce any systematic bias to our results. We also note the limitations inherent to any statistical modeling and multivariate adjustment. Although we only included the most important clinical variables likely to cause confounding during statistical modeling, we recognize the potential for over-fitting of the statistical model. However, we note that in usual clinical care it is rare for diagnostic tests to be used in any other than the unadjusted form.

**Table 5** HRs for Death or MI Stratified by H-FABP Results Among Troponin-Negative Patients

Unadjusted	HR (95% CI)	p Value
H-FABP 0.15–3.26 $\mu\text{g/l}$	1.00	<0.001
H-FABP 3.27–6.48 $\mu\text{g/l}$	3.46 (1.69–7.10)	0.001
H-FABP 6.49–12.77 $\mu\text{g/l}$	11.20 (4.95–25.36)	<0.001
H-FABP 12.78–151.0 $\mu\text{g/l}$	16.64 (2.21–125.51)	0.006
Adjusted for Age and Serum Creatinine	Adjusted HR (95% CI)	
H-FABP 0.15–3.26 $\mu\text{g/l}$	1.00	0.01
H-FABP 3.27–6.48 $\mu\text{g/l}$	1.55 (0.72–3.36)	0.26
H-FABP 6.49–12.77 $\mu\text{g/l}$	3.12 (1.11–8.76)	0.03
H-FABP 12.78–151.0 $\mu\text{g/l}$	16.67 (2.19–127.06)	0.007

Abbreviations as in Tables 1 and 4.

We report here results for biomarkers measured at only 1 time-point (i.e., >12 h from symptom onset). This was our pre-stated objective and is in keeping with standard practice in our institution and indeed most other hospitals in the United Kingdom. Initial risk stratification of patients into high and low risk was done primarily on the basis of clinical and ECG parameters rather than admission biomarker assessment. The likelihood of a false negative troponin in our study is very low, because of the high precision of the Ultra-TnI (Siemens Healthcare Diagnostics) when run in a single batch. Patients recruited into the study also had an earlier serum sample collected at the time of first contact with the emergency department whenever logistically possible. Future analyses will assess the value of H-FABP (and other cardiac markers) measured at this earlier time point in the early diagnosis of MI in detail. Limited analyses of the 384 troponin-negative patients who had an admission serum sample collected (of the 756 troponin-negative patients in the study [i.e., 50%]) showed that the occurrence of death or MI among those with raised H-FABP at the time of admission (male >5.8 µg/dl, female >5.3 µg/dl) was 22.2% (6 of 27 patients) as compared with a much lower event rate of 5.3% in patients with normal H-FABP at admission (19 of 357 patients), which was statistically significant ( $p = 0.001$ ) (HR: 5.08, 95% CI: 1.84 to 14.07,  $p = 0.002$ ).

We also note the substantial influence of the troponin results in deciding further management, as illustrated by the very low rate of inpatient coronary angiography in troponin-negative patients (Table 2). This underlines the importance of using the new ultra-sensitive troponin assays and classifying all patients with troponin values >99th percentile value as potentially high risk. Importantly, many centers around the world have yet to make this change, and our data indicate that this would be improved further by the parallel measurement of H-FABP with a similarly high-precision, high-sensitivity assay. The multimarker cardiac biochip that we used in this study (Randox Laboratories, Ltd.) permits such parallel measurements to be easily made. Furthermore, the recent development of a point-of-care platform permits rapid delivery of results and repeat measurements. Further studies will assess the value of this system in the context of suspected ACS and also in the detection of myocardial ischemia and injury in other contexts, such as after PCI or surgical intervention.

The H-FABP seems to provide direct evidence of myocardial ischemia even when frank myocyte necrosis is absent (18,19). Meng et al. (18) demonstrated that in rats the H-FABP concentration in peripheral blood was 4 times the baseline after just 15 min of induced myocardial ischemia. Additionally, in human autopsy cases it was possible to demonstrate depletion of H-FABP in the myocardium of individuals dying suddenly after the onset of chest pain. These changes were present despite the absence of myocyte necrosis on electron microscopy (19). This caused those investigators to conclude that H-FABP is both a sensitive

and an early marker of myocardial ischemia. Such a conclusion is intuitive, given that H-FABP is confined to the cytoplasm and also because of its small molecular size, because both these features permit early leakage through the porous membranes of ischemic myocardial cells. This might explain the strong correlation between H-FABP and ST-segment depression noted on ECG (Table 1). The presence of myocardial ischemia resulting in chest pain might result from coronary spasm in the presence of atheroma but in the absence of plaque erosion/rupture and thrombus formation. Such patients might be expected to have no detectable troponin and yet have an elevated H-FABP and, importantly, an increased risk of future major cardiovascular event.

## Conclusions

We have demonstrated that the prognostic value of elevated H-FABP is additive to troponin in low- and intermediate-risk patients with suspected ACS. Importantly, this is true in spite of use of a very-high-sensitivity troponin assay that achieves the analytical performance prescribed in the Universal Definition of MI consensus document (10). We interpret this as supporting the role of H-FABP as a marker of myocardial ischemia, even in the absence of frank necrosis.

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**Key Words:** acute coronary syndrome ■ heart-type fatty acid-binding protein ■ mortality ■ myocardial infarction ■ troponin.

ORIGINAL ARTICLE

# Troponin T and Heart Type Fatty Acid Binding Protein (h-Fabp) as Biomarkers in Patients Presenting with Chest Pain

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**Abstract** Acute coronary syndrome (ACS) is a term for a range of clinical signs and symptoms suggestive of myocardial ischemia. It results in functional and structural changes and ultimately releasing protein from injured cardiomyocytes. These cardiac markers play a major role in diagnosis and prognosis of ACS. This study aims to assess the efficacy of heart type fatty acid binding protein (h-FABP) as a marker for ACS along with the routinely used hs-TropT. In our observational study, plasma h-FABP (cut-off 6.32 ng/ml) and routinely done hs-Trop T (cutoff 0.1 and 0.014 ng/ml) were estimated by immunometric laboratory assays in 88 patients with acute chest pain. Based on the clinical and laboratory test findings the patients were grouped into ACS ( $n = 41$ ) and non-ACS ( $n = 47$ ). The diagnostic sensitivity, specificity, NPV, PPV and ROC curve at 95 % CI were determined. Sensitivity of hs-TropT (0.1 ng/ml), hs-TropT (0.014 ng/ml) and h-FABP were 53, 86 and 78 % respectively and specificity for the same were 98, 73 and 70 % respectively. Sensitivity, specificity and NPV calculated for a cut-off

combination of hs-TropT 0.014 ng/ml and h-FABP was 100, 51 and 100 % respectively. These results were substantiated by ROC analysis. Measurement of plasma h-FABP and hs-TropT together on admission appears to be more precise predictor of ACS rather than either hs-Trop T or h-FABP.

**Keywords** Acute coronary syndrome · Heart type fatty acid binding protein (h-FABP) · High sensitive Troponin T (hs-TropT) · Cardiac markers

## Introduction

Acute coronary syndrome (ACS) refers to a constellation of clinical symptoms caused by acute myocardial ischemia. Patients with ACS are subdivided into two major categories based on the 12-lead electrocardiogram (ECG) at presentation, those with ST-elevation myocardial infarction (STEMI) and those who present with ST-segment depression, T-wave changes, or no ECG abnormalities (non-ST elevation ACS, NSTEACS). The latter term NSTEACS includes both unstable angina and non-ST elevation myocardial infarction (NSTEMI) [1], which can be detected through biomarkers for myocardial necrosis.

Myocardial necrosis is accompanied by the release of structural proteins and other intracellular macromolecules into the cardiac interstitium as a result of compromise of the integrity of cellular membranes [1]. Biomarkers of myocardial necrosis include cardiac Troponin I and T (TropI and TropT), creatine phosphokinase and isoenzymes, heart type fatty acid binding protein (h-FABP) [2] and myoglobin [3]. Currently, on the basis of improved sensitivity and superior tissue-specificity compared with the other available biomarkers of necrosis, troponins are

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the preferred biomarker for the detection of myocardial injury [4]. Troponins typically increase more than 20 times above the upper limit of the reference range in myocardial infarction (MI) as compared to creatine kinase MB (CKMB) which usually increases ten times above the reference range. The troponins begin to elevate 3 h from the onset of chest pain in MI. And because of the continuous release, troponin elevation persists for days. This prolonged course with troponin is advantageous for the late diagnosis of MI; however, it limits the diagnosis of early infarction [2].

Fatty acid binding proteins (FABP) are small (12–15 kDa) cytoplasmic proteins that have diverse tissue distribution and concentration in different organs, diverse isoelectric point (PI), binding capacity and binding specificity [5]. These are abundantly expressed in tissues with an active fatty acid metabolism such as heart and liver. The primary function of FABP is facilitation of intracellular long-chain fatty acid transport [6]. Heart-type fatty acid-binding protein (h-FABP) is a low molecular weight (14.5 kDa) protein, which contains 132 amino acid residues [7]. h-FABP is found in abundance in cardiomyocytes but is also expressed (to a lesser extent) in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands and placenta [8]. h-FABP binds two molecules of fatty acids and is involved in the delivery of fatty acyl coenzyme A, which is actively included in oxidation processes, which generate energy in the mitochondria. The concentration of fatty acids in plasma and in myocardial tissue rise during myocardial ischemia and it is postulated that h-FABP, which is immediately available for the metabolic needs of the cell, protects myocytes against fatty acid oxidation. Following myocardial cell damage, this small protein diffuses much more rapidly than troponins through the interstitial space and appears in the circulation probably through a trans-endothelial pathway [9]. This protein can be detected in the blood as early as 1–3 h after onset of chest pain, with peak values reached at 6–8 h and plasma levels returning to normal within 24–30 h [10]. Thus, h-FABP appears to be a very stable protein for early detection of myocardial necrosis and can be useful for in vitro clinical diagnostic purposes.

Recent studies have shown that h-FABP might have potential as an early cardiac biomarker in latent myocardial injury. It can be used for prognosis in chronic heart failure patients [11], and also to detect myocardial damage within 1 h after onset of ischemia [12]. However, the clinical impact of this on its diagnostic performance remains uncertain [13]. This study aims to validate the immunoturbidimetric quantitative in vitro determination of h-FABP and to compare its levels to routinely measured Troponin T levels in early diagnosis of patient presenting with acute chest pain in emergency department in a tertiary care hospital.

## Methods

### Study Population

The study was carried out in the Department of Biochemistry, P. D Hinduja National Hospital and Medical Research Centre, Mumbai, India. Patients arriving at the emergency department with chest pain or pain radiating to left arm, epigastric pain, shortness of breath and other symptoms indicative of ACS were recommended to perform biomarker test for Troponin T by the cardiologists. These patients were then also analysed for h-FABP. Symptom onset was recorded for each patient at the time of admission. Demographics, including body mass index (BMI) and clinical data, such as, ECG recordings, Systolic and diastolic blood pressures diagnosis, revascularization, and coronary risk factors were collected from hospital medical records.

### Final Diagnosis

Diagnostic outcome was categorized into two groups: (1) ACS [which included Unstable Angina (UA), STEMI, and non-STEMI]; (2) No ACS [which included cases of non-cardiac chest pain (NCCP), epigastric pain, left leg/arm pain etc.]. The diagnosis of NCCP was based on absence of significant findings indicative of cardiovascular problems, laboratory tests and ECG findings.

### Sample Collection and Biochemical Analysis

Blood samples drawn in EDTA vacutainer from the patients admitted to the Emergency department were sent to the biochemistry laboratory for Troponin T (hs-TropT) estimation. Plasma TropT levels were measured quantitatively using the Elecsys high sensitive Troponin T (hs-TropT) immunoassay (Roche Diagnostics, Switzerland) using 912 Roche analyzer. For this study, two different cut-off values of 0.1 ng/ml recommended by WHO and 0.014 ng/ml recommended in kit insert by the manufacturers were used to compare the results. As analysis of h-FABP was not done immediately after hs-TropT estimation, these samples were stored at –80 °C till h-FABP test was performed.

Estimations of h-FABP assay (Randox Laboratories Ltd., Crumlin, UK) was done on VITROS® 5, 1 FS Chemistry System, (Ortho-Clinical Diagnostics, Johnson & Johnson Limited) using bi-level quality control material and calibrators supplied with the assay kit. The analytical range for h-FABP is 0.75–120 ng/ml; a cut-off of 6.32 ng/ml was used to define abnormality based on 99th percentile for the 250 healthy controls as per the kit inserts.

**Table 1** Baseline clinical data of subjects in the study population

Characteristic	All subjects (n = 88)	Subjects with ACS (n = 41)	Subjects without ACS (n = 47)	P value	Significance
Age (mean years ± SD)	58.7 ± 16.2	64.6 ± 14.4	53.6 ± 15.7	0.44	NS
Male, n (%)	51 (58)	25 (61)	26 (55)	0.85	NS
Female, n (%)	37 (42)	16 (39)	21 (45)	0.72	NS
Risk factors					
Hypertension, n (%)	45 (51)	22 (54)	23 (49)	0.65	NS
Diabetes, n (%)	22 (25)	13 (32)	9 (19)	0.18	NS
Smoking, n (%)	11 (13)	7 (17)	4 (9)	0.23	NS
Renal disease, n (%)	5 (6)	3 (7)	2 (4)	0.54	NS
Previous interventions, n (PCI/CABG) (%)	14 (16)	10 (24)	4 (9)	0.05	S
Clinical findings					
Heart rate (beats/min) (mean ± SD)	91.6 ± 25.3	95.3 ± 32.1	88 ± 19.18	—	—
Blood pressure (mmHg) (mean ± SD)					
Diastolic	84.9 ± 5	83.9 ± 20.6	84.9 ± 20.4	—	—
Systolic	131.1 ± 26.1	134.5 ± 23.6	136.1 ± 25.9	—	—
Creatinine (mg/dl) (mean ± SD)	1.4 ± 1.3	1.3 ± 1.4	1.5 ± 1.8	—	—

ACS acute coronary syndrome, PCI percutaneous coronary interventions, CABG coronary artery bypass graft, SD standard deviation, NS non-significant, S significant

**Table 2** Bio-statistical analysis of cardiac markers in ACS patients

	ACS (n = 41)	Non-ACS (n = 47)	Sensitivity (%) (95 % CI)	Specificity (%) (95 % CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)
<b>Trop T (cut off 0.1 ng/ml)</b>						
≥0.1	TP = 22	FP = 1	53 (37.4–69.3)	98 (88.7–99.6)	96 (77.9–99.3)	71 (58.2–81.4)
≤0.1	FN = 19	TN = 46				
<b>Trop T (cut off 0.014 ng/ml)</b>						
≥0.014	TP = 35	FP = 13	86 (70.8–94.4)	73 (57.4–84.4)	73 (58.2–84.7)	85 (70.2–94.3)
≤0.014	FN = 6	TN = 34				
<b>h-FABP (cut off 6.32 ng/ml)</b>						
≥6.32	TP = 32	FP = 14	78 (62.4–89.4)	70 (55.1–82.6)	70 (54.2–82.3)	79 (63.2–89.7)
≤6.32	FN = 9	TN = 33				

ACS acute coronary syndrome, PPV positive predictive value, NPV negative predictive value CI confidence interval, TP true positive, FP false positive, TN true negative, FN false negative

## Statistical Analysis (Table 2, 3)

Categorical variables are presented as numbers and percentages, while continuous variables are presented as mean ± SD (Standard deviation). Variables were compared using z-transformation test, Chi squared test and Mann–Whitney U test. All hypothesis were 2-tailed tests and P < 0.05 was considered statistically significant. Area under the receiver operator characteristic (ROC) curves at 95 % confidence interval (CI) was calculated using MedCalc Statistical Software (MedCalc version 12, Mariakerke, Belgium).

## Results

Of the 88 patients, 41 (46.9 %) were diagnosed with ACS at admission. Patients with a final diagnosis of ACS did not differ significantly from those without ACS with respect to mean age, gender, risk factors like hypertension, diabetes, smoking, renal disease, previous interventions (Table 1).

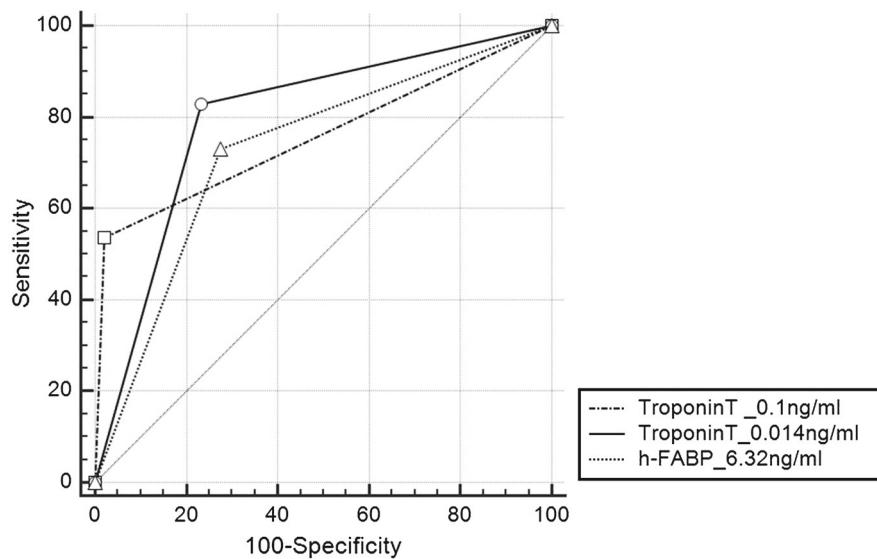
In this study, two different diagnostic cut-offs were used for hs-Trop T, 0.1 and 0.014 ng/ml respectively, to compare the performance of the assay. The specificity of hs-TropT >0.1 ng/ml (98 %) is significantly higher than Troponin T >0.014 ng/ml (73 %) and h-FABP >6.32 ng/ml

**Table 3** Bio-statistical analysis of cardiac markers in combination for ACS patients

ACS (n = 41)	Non-ACS (n = 47)	Sensitivity (%) (95 % CI)	Specificity (%) (95 % CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)
<b>Trop T (cut off 0.1 ng/ml) and/or h-FABP (cut off 6.32 ng/ml)</b>					
≥0.1	TP = 37	FP = 15	90 (76.9–97.2)	68 (52.9–80.9)	71 (56.9–82.9)
≤0.1	FN = 4	TN = 32			89 (73.9–96.8)
<b>Trop T (cut off 0.014 ng/ml) and/or h-FABP (cut off 6.32 ng/ml)</b>					
≥0.014	TP = 41	FP = 23	100 (91.3–100)	51 (36.1–65.9)	64 (51.1–75.7)
≤0.014	FN = 0	TN = 24			100 (91.7–100)

ACS acute coronary syndrome, *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval, *TP* true positive, *FP* false positive, *TN* true negative, *FN* false negative

**Fig. 1** Comparative receiver operator characteristic (ROC) curve for individual markers, Troponin T and h-FABP



	AUC	SE	95% CI
Trop T (0.014ng/ml)	0.798	0.0431	0.699 to 0.876
Trop T (0.1ng/ml)	0.758	0.0408	0.655 to 0.843
h-FABP (6.32ng/ml)	0.728	0.0481	0.622 to 0.817

Note – **AUC:** Area Under the receiver Operator Characteristic Curve, **SE:** Standard Error,

**CI:** Confidence Interval

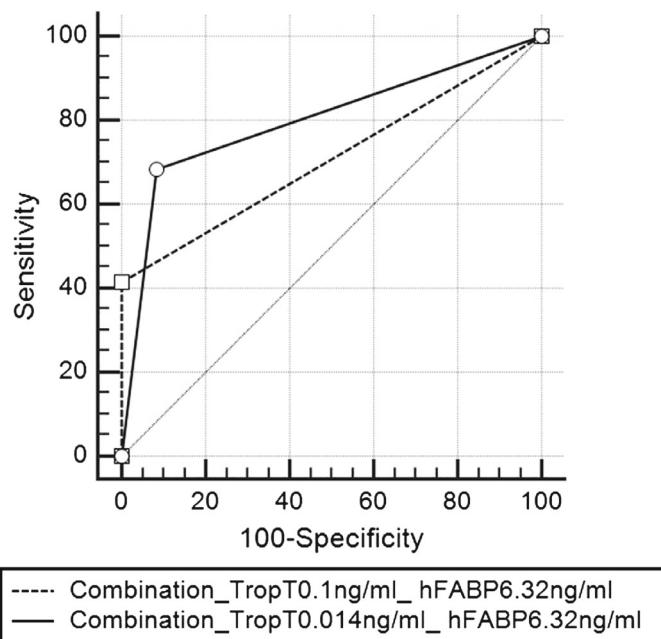
(70 %). In contrast, h-FABP >6.23 ng/ml and Troponin T >0.014 ng/ml was more sensitive than Troponin T >0.1 ng/ml with sensitivities equal to 78, 86 and 53 % respectively. Table 2 shows that Troponin T > 0.014 ng/ml is superior to Troponin T >0.1 ng/ml and h-FABP in terms of accuracy.

A combination of h-FABP (>6.32 ng/ml) OR Trop T (>0.014 ng/ml) was found to be optimal for early diagnosis of ACS, comparing with the combination of h-FABP

(>6.32 ng/ml) OR Trop T (>0.1 ng/ml) as the former gives a sensitivity and NPV of 100 % (Table 3).

The area under the ROC curve to distinguish ACS from non-ACS after the symptom onset was, 0.758 for TropT (0.1 ng/ml), 0.798 for TropT (0.014 ng/ml) and 0.728 for h-FABP (Fig. 1). And in combination, area under the curve (AUC) for TropT (0.1 ng/ml) and h-FABP was 0.707 whereas for TropT (0.014 ng/ml) and h-FABP was 0.799 (Fig. 2).

**Fig. 2** Comparative receiver operator characteristic (ROC) curve in combination of markers, Troponin T and h-FABP



Note – **AUC:** Area Under the receiver Operator Characteristic Curve, **SE:** Standard Error, **CI:** Confidence Interval

## Discussion

This observational study demonstrated that measurement of plasma h-FABP in accordance with Troponin T concentrations on admission provides important information for risk stratification of patients presenting with ACS after the onset of chest pain. Importance of biomarkers, both in diagnosis and prognosis of ACS is now well established [2] and proved superior to electrocardiographic guidance alone [8]. Cardiac troponins remain the cornerstone in the risk stratification of patients with suspected ACS [14]. h-FABP has been reported to be particularly sensitive within the first few hours after the onset of coronary occlusion and symptoms. The reason for this sensitivity has been explained by its small molecular weight (15 kDa) and its cytoplasmic unbound abundance, resulting in rapid release from damaged myocardium. Authors [7, 10, 15] have reported sensitivity and specificity as 42–67 % and 95–97 %

respectively for troponin whereas for h-FABP, 75–87 % and 89–93 %, in patients admitted with 6 h of chest pain onset. Our study result was in complete agreement with the above studies presenting with 53 and 97 % sensitivity and specificity for Troponin T and 78 and 70 % for h-FABP respectively.

The low h-FABP specificity of 42–70 % in similar settings was also reported by number of other investigators [7, 10, 15–17]. The reasons for the poor specificity of h-FABP for the final diagnosis of AMI have been due its presence in tissues outside the heart or may be because renal insufficiency [18].

In accordance with our study, an increased sensitivity in combination of hs-TropT measurement with h-FABP has been discussed in other reports [3, 15, 18]. Also, ROC curves demonstrated that a combined measurement of plasma h-FABP and Troponin T, has a great potential which allows to discriminate between ACS and non-ACS

patients as compared to the conventional measurement of both markers individually.

## Conclusion

The present study highlights the importance of estimating both cardiac markers (h-FAPB and hs-Trop T) in early diagnosis of ACS. Furthermore, in cases present at the emergency department after the chest pain onset, combined use of Troponin T and h-FABP is optimal for improving the early diagnosis of ACS. Also, the 100 % NPV at this time point may improve the accuracy of discharge decisions of the patients. The small sample size can be a limitation of the study which prevent generalisation of results. However, further large scale studies would certainly help to access the value of the combined use of these markers in the context of suspected ACS, and to detect myocardial ischemia and injury, such as after PCI or surgical interventions.

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Available online at [www.sciencedirect.com](http://www.sciencedirect.com)**ScienceDirect**journal homepage: [www.elsevier.com/locate/ihj](http://www.elsevier.com/locate/ihj)**Original Article****Heart-type fatty acid-binding protein (H-FABP)  
as an early diagnostic biomarker in patients  
with acute chest pain**

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**ABSTRACT**

**Background:** Heart-type fatty acid-binding protein (H-FABP) is an emerging biomarker, which was found to be sensitive for the early diagnosis of acute myocardial infarction (AMI). We prospectively investigated the usefulness of H-FABP determination for the evaluation of acute chest pain in patients arriving at the emergency department.

**Methods:** Fifty-four patients presenting with acute ischemic chest pain were evaluated. H-FABP was estimated at admission using latex-enhanced immunoturbidimetric assay. Serial cardiac troponin I (cTnI), creatinine kinase-MB (CK-MB) determination, ischemia workup with stress testing, and/or coronary angiogram (CAG) were performed according to standard protocols.

**Results:** The sensitivity and specificity of H-FABP was 89.7% and 68%, for cTnI it was 62.1% and 100%, and for CK-MB it was 44.8% and 92%, respectively for diagnosis of AMI. The sensitivity of H-FABP was found to be far superior to initial cTnI and CK-MB, for those seen within 6 h (100% vs. 46.1%, 33% respectively). On further evaluation of patients with positive H-FABP and negative cTnI, 71.4% of the patients had significant lesion on CAG, indicating ischemic cause of H-FABP elevation. Six patients with normal cTnI and CK-MB with high H-FABP had ST elevation on subsequent ECGs and were taken for primary angioplasty.

**Conclusion:** H-FABP is a highly sensitive biomarker for the early diagnosis of AMI. H-FABP as early marker and cTnI as late marker would be the ideal combination to cover the complete diagnostic window for AMI. Detection of myocardial injury by H-FABP may also be applied in patients with unstable angina. H-FABP can also be used as a marker for early detection of STEMI before the ECG changes become apparent.

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## 1. Introduction

The clinical evaluation, triage, and management of patients with possible acute coronary syndromes (ACS) present a substantial medical and fiscal challenge.

Cardiac troponin (cTn) is recommended as the preferred biomarker for early risk stratification.<sup>1</sup> cTn may not rise for the first 6 h after the onset of symptoms and, if negative, should be repeated within 8–12 h after the onset of pain.<sup>1</sup>

Application of an early biomarker potentially reduces diagnostic uncertainty in patients suspected of an ACS. This may lead to a reduction in unnecessary ICU admissions, patient's financial burden, hospital resources, and healthcare costs. Moreover, a diagnosis of ACS can be established much earlier than with troponin, which may result in earlier initiation of appropriate treatment, including revascularization procedures.

Heart-type fatty acid-binding protein (H-FABP) is a novel biomarker shown to be released from injured myocardium and detected in blood within 1 h after onset of ischemia.<sup>2</sup> Several studies have shown that it is a sensitive early marker of myocardial injury.<sup>3–8</sup>

This study was designed to evaluate the efficacy of serum H-FABP measurement for triaging of patients presenting to the emergency department with chest pain, in comparison to cardiac troponin I (cTnI) and creatinine kinase-MB (CK-MB).

## 2. Materials and methods

### 2.1. Study design

The study is a prospective observational study conducted in Amrita Institute of Medical Sciences, Kerala, India. The study was approved by the institutional ethical committee. From August 2013 to July 2014, 77 patients with acute chest pain presenting to the emergency department were enrolled and their data entered into a clinical database after obtaining informed, written consent. Inclusion criteria included men and women aged 18 years or older, with chest pain suggestive of cardiac ischemia at the discretion of the treating cardiologist. Patients with non-cardiac chest pain, renal insufficiency with an estimated glomerular filtration rate (eGFR) <60 ml/min, symptoms temporally related to direct local trauma of <3 days, ECG changes suggestive of STEMI at presentation, new onset dysrhythmia excluding sinus tachycardia, new onset congestive heart failure, acute pulmonary edema, recent cardiopulmonary resuscitation, liver disease, and sepsis were excluded from the study.

Important definitions related to inclusion and exclusion criteria are as follows: chest pain suggestive of coronary origin is defined, in accordance with ACC/AHA guidelines,<sup>1</sup> as chest or left arm pain as the chief symptom. Non-cardiac chest pain is defined at the discretion of the cardiologist after evaluation using radiography or other technical assessments. Acute myocardial infarction (AMI) was diagnosed if there is biochemical evidence of cardiac myocyte necrosis in the appropriate clinical setting as per the ESC/ACCF/AHA/WHF universal definition of myocardial infarction.<sup>9</sup> Patients with

reduced renal clearance (eGFR <60 ml/min) were excluded due to higher pre-infarct baseline H-FABP levels.<sup>4</sup> Patients with a history of trauma less than 3 days were excluded due to potential elevation in H-FABP with muscle injury. Patients with ST elevation on ECG, heart failure, dysrhythmias, pulmonary edema, hypotension, or cardiopulmonary resuscitation were excluded due to potential early triaging and a potential inability to follow these patients throughout the study period.

### 2.2. Study protocol

Information regarding patient demographics and relevant clinical data, such as that concerning the patient's cardiac history and contact address, was recorded on a data collection sheet. Blood samples were taken upon arrival to the Casualty. All blood tubes for biomarker determination were obtained using clot activator tubes, centrifuged immediately at 3000 rpm for 5 min, and the serum was analyzed.

### 2.3. Tests

A latex-enhanced immunoturbidimetric assay via Olympus AU2700 for H-FABP was used, with an upper limit of normal of 6.4 ng/L as recommended by the manufacturer (Randox Laboratories, UK). H-FABP was estimated only at admission. cTnI was measured using Abbott Architect-Chemiluminescence method on admission, and at 6th and 12th hours post-admission as part of the standard chest pain protocol, and a cut-off value of 0.14 ng/ml was taken with a 99th percentile reference range as recommended by ACC/AHA.<sup>1</sup> A diagnosis of myocardial infarction was made if cTnI measured 12 h after admission was greater than the upper limit of normal. Serum CK-MB was estimated by photometric method on admission, and at 6th and 12th hours post-admission as part of the standard chest pain protocol along with cTnI.

Possible myocardial ischemia was evaluated with myocardial stress imaging and/or coronary angiography. Stress test was performed in conjunction with ECHO imaging. Coronary angiography was carried out in those patients with positive stress testing or those patients deemed to have a high-pretest probability for coronary artery disease (CAD) based on subsequent cTnI results. All angiographic images were reviewed by experienced cardiologists. A positive coronary angiography is defined as stenosis resulting in ≥50% diameter reduction in any major epicardial vessel. Final diagnosis was based on the discharge diagnosis documented on discharge summaries.

### 2.4. Statistics

Continuous variables were presented as mean ± SD, and categorical variables as frequencies (percentages). Comparisons for categorical variables were performed using McNemar test. The sensitivity, specificity, and positive and negative predictive values were calculated to assess the diagnostic accuracy of H-FABP, cTnI, and CK-MB in the exclusion of ACS on admission and at 6th and 12th hours post-admission for cTnI and CK-MB. Sensitivity of H-FABP, cTnI, and CK-MB was compared using Z-test statistic for proportion. All statistical

**Table 1 – Risk factors (n = 54).**

Risk factors	n	%
Severe angina	8	14.8
Family history of CAD	7	13.0
Hypertension	34	63.0
Dyslipidemia	31	57.4
Type 2 DM	34	63.0
Current smoker	2	3.7
Known case of CAD	25	46.3
Aspirin use with in last 24 h	24	44.4
ST deviation	23	42.6
Increased markers (standard markers)	29	53.7

analyses were performed using the IBM SPSS version 20.0 software package (IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY: IBM Corp).

### 3. Results

Seventy-seven patients were evaluated in the casualty and H-FABP was estimated. 23 patients were excluded from the study after further evaluation because of the various causes (renal failure, liver disease, sepsis, etc.). The mean age was 63.4 ± 11.5 years and 68.5% were men. The risk factors are summarized in Table 1. Hypertension, type 2 diabetes, and history of CAD account for 63%, 63%, and 46.3%, respectively. TIMI risk score for unstable angina/NSTEMI was calculated based on the risk factors on presentation. 25.9% of patients had TIMI risk score of 2. Majority of the patients had TIMI risk score

between 2 and 4. 53.7% of patients presented within 6 h of onset of chest pain. Though majority of patients were clear about the history of duration of pain, few patients gave history of vague pain, which had started few days previously and increased gradually. In such patients, the time from onset of initial chest discomfort was taken as duration of chest pain. 15 (27.8%) patients had regional wall motion abnormality on echocardiography. Coronary angiogram (CAG) was done in 40 (74.1%) patients.

Only patients with NSTEMI, positive stress test, or patients with high-clinical suspicion underwent CAG. Out of the 40 patients who underwent CAG, 32 (59.3%) patients had significant disease. Table 2 summarizes the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of H-FABP, cTnI, and CK-MB on admission with relation to duration of chest pain.

The sensitivity of H-FABP was found to be superior to initial cTnI (89.7% vs. 62.1%, Z = 4.61, p < 0.01) and CK-MB (89.7% vs. 44.8%, Z = 6.90, p < 0.01). In patients presenting within 6 h after onset of chest pain, the sensitivity of H-FABP was found to be far superior to initial cTnI (100% vs. 46.1%, Z = 8.93, p < 0.01), and CK-MB (100% vs. 33.3%, Z = 10.40, p < 0.01), but the specificity of H-FABP for AMI was poor (68%). Table 3 summarizes sensitivity and specificity of various markers serially done after admission.

In five out of the seven patients with positive H-FABP and negative cTnI, CAG was done based on either positive stress test or high-clinical suspicion of CAD. All the 5 patients had significant lesion on CAG indicating ischemic cause of H-FABP elevation. Rest of the 2 patients had a negative stress test.

**Table 2 – Comparison of admission cardiac markers with relation to duration of chest pain (n = 54).**

	Duration of chest pain								
	≤6 h (n = 29)			>6 h (n = 25)			Total (n = 54)		
	H-FABP	cTnI	CK-MB	H-FABP	cTnI	CK-MB	H-FABP	cTnI	CK-MB
Sensitivity	100%	46.1%	33.3%	78.6%	78.6%	57.1%	89.7%	62.1%	44.8%
Specificity	85.7%	100%	92.9%	45.5%	100%	90.9%	68%	100%	92.0%
Accuracy	93.1%	72.4%	62.1%	64%	88%	72%	79.6%	79.6%	66.7%
PPV	88.2%	100%	83.3%	64.7%	100%	88.9%	76.5%	100%	86.7%
NPV	100%	63.6%	56.5%	62.5%	78.6%	62.5%	85%	69.4%	59%

H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; CK-MB, creatinine kinase-MB; PPV, positive predictive value; NPV, negative predictive value.

**Table 3 – Comparison of cardiac markers serially done after admission (n = 54).**

	On hospital admission (n = 54)			6 h after hospital admission (n = 54)		12 h after hospital admission (n = 54)	
	H-FABP	cTnI	CK-MB	cTnI	CK-MB	cTnI	CK-MB
Sensitivity	89.7%	62%	44.8%	96.6%	75.9%	100%	79.3%
Specificity	68%	100%	92%	100%	96%	100%	92%
Accuracy	79.6%	79.6%	66.7%	98.1%	85.2%	100%	85.2%
PPV	76.5%	100%	86.7%	100%	95.7%	100%	92%
NPV	85%	69.4%	59%	96.2%	77.4%	100%	79.3%

H-FABP was estimated only on admission and was not repeated thereafter. cTnI estimated 12 h after hospital admission was assumed to be the gold standard and hence the 100% accuracy. H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; CK-MB, creatinine kinase-MB; PPV, positive predictive value; NPV, negative predictive value.

#### 4. Discussion

Early diagnosis of AMI facilitates rapid and appropriate triage of patients within the Accident and Emergency department, helping to prevent inadvertent discharge of patients with AMI. It also avoids delay in administering treatment for AMI, and reduces the possibility of patients without AMI given treatments from which they will not benefit, and which have the potential to cause significant harm. The 12-lead ECG is an important tool for early detection of AMI, but it has significant limitations, e.g., LBBB or a permanent pacemaker may make interpretation impossible and ECG changes may not be apparent early in the course of the disease. Another significant factor is that interpretation of the 12-lead ECG is dependent on the experience of the physician.<sup>10</sup>

AMI is diagnosed if there is biochemical evidence of cardiac myocyte necrosis in the appropriate clinical setting.<sup>9</sup> Cardiac troponins have assumed an important role in modern cardiology practice, both in diagnosis of AMI and in risk stratification of patients with acute chest pain. A major drawback with cardiac troponins is that they are released relatively slowly from damaged myocytes.<sup>11</sup> This study confirms the limitation of sampling cardiac troponin at the time of admission for patients presenting with acute ischemic-type chest pain. The sensitivity of initial cTnI on admission was 62%. The sensitivity of initial troponin was at its lowest for patients who presented within 6 h of symptom onset (46.1%) (Table 2). It increased with increasing time from symptom onset to admission, with a sensitivity of 78.6% for patients who presented after 6 h of onset of chest pain. This leaves a false negative rate of 21.4% for the initial cTnI even in patients who presented 6 h after the onset of chest pain (i.e., subsequent cTnI sampled later from admission becoming positive) (Table 3). These findings were similar to a study by McCann et al. where the sensitivity of initial cardiac troponin T (cTnT) for AMI was found to be 75%. The sensitivity of initial cTnT for patients who presented within 4 h of symptom onset was 55%.<sup>14</sup>

This study has demonstrated that, of all the investigational biomarkers, H-FABP has a potential role in the very early diagnosis of AMI. There has been interest in H-FABP as a biochemical marker of myocardial injury since 1988, when it was demonstrated to be released from injured myocardium.<sup>12</sup> The release characteristics of H-FABP after AMI show that a rise is detectable as early as 1 h after symptom onset, a peak level is reached after 2–4 h, and due to rapid renal clearance, the level returns to baseline within 16–24 h.<sup>2,13</sup> Several studies reporting the usefulness of H-FABP as an early marker of AMI pre-dated the widespread use of cardiac troponins.<sup>3–8</sup> Data for the diagnostic performance of admission of H-FABP using the modern definition of AMI are limited.

Our study has demonstrated that measurement of H-FABP in patients with acute ischemic-type chest pain at the time of admission is useful and complements the subsequent measurement of cardiac troponin. The sensitivity and specificity of H-FABP in our study were 89.7% and 68%, respectively. The sensitivity of H-FABP is superior to initial cTnI for those seen within 6 h (100% vs. 46.1%,  $Z = 8.93$ ,  $p < 0.01$ ), but the specificity of H-FABP for AMI was poor (68%) (Table 2). The

specificity of H-FABP for AMI reported in previous studies varies from 49% to 86%.<sup>3–8,14,15</sup> In a study by Chan et al., H-FABP had better sensitivity and NPV on admission (72% and 67%, respectively) than cTn (51% and 51%, respectively). Furthermore, the sensitivity and NPV of H-FABP increased to 100% for samples taken 1 h after admission.<sup>15</sup> A study by Ruzgar et al.<sup>4</sup> showed 38% sensitivity with troponin, 76% sensitivity with CK-MB, and 95% sensitivity with H-FABP in patients admitted within 6 h of chest pain onset. Within 6–24 h, sensitivity of troponin and CK-MB increased to 100 and 90% respectively, while that of H-FABP was 91%.

The sensitivity of H-FABP was also found to be superior to CK-MB in the early diagnosis of AMI in the present study. The sensitivity of CK-MB in our study was found to be 44.8%. In patients who presented within 6 h, the sensitivity was even lower (33.3%), whereas the specificity of CK-MB was higher compared to H-FABP (92% vs. 68%) (Table 2). Recently, a high-sensitivity troponin T (hsTnT) assay has been developed, permitting measurement of concentrations that are 10-fold lower than those measurable with conventional assays.<sup>16,17</sup> Though hsTnT assay offers excellent diagnostic performance to rule out ACS, a recent study by Inoue et al. showed that it is prone to more false-positive results compared to H-FABP with similar overall diagnostic performance.<sup>18</sup>

The reason for the relatively poor specificity of H-FABP in the current study may relate to a number of factors. Firstly, H-FABP was estimated in all the patients regardless of the duration of chest pain. As the level returns to base-line within 20 h due to rapid renal clearance, it is unlikely to be positive in patients presenting after 20 h of chest pain onset unless they had a re-infarct. Though the overall specificity was only 68%, the specificity in patients presenting within 6 h of chest pain was 85.7%, indicating that the low specificity is due to plasma kinetics (Table 2). Secondly, H-FABP may be released from ischemic myocardium, as well as infarcted myocardium. In our study on further evaluation, five out of the seven patients with positive H-FABP and negative cTnI had significant lesion on CAG indicating ischemic cause of H-FABP elevation. Thirdly, H-FABP is present, albeit at lower concentrations, in skeletal muscle. In this study, no data were collected on recent physical exercise, recent injury, or recent intramuscular injections.

Out of the 54 patients included in the study, 6 patients with normal cTnI and CK-MB with high H-FABP at presentation had new onset ST elevation, 1–2 h after hospital admission, and underwent primary angioplasty. These results indicate the potential for H-FABP for early diagnosis of STEMI even before the ECG changes develop. All these patients had very high H-FABP values (>100) with normal troponin and CK-MB.

##### 4.1. Limitations

A limitation of this study is that recruitment took place at the time of admission from casualty of a tertiary care hospital with cardiology specialization. This is reflected in the relatively high incidence of AMI (53.7%). As a consequence, the results presented may not necessarily be applicable to lower risk populations, such as all patients with chest pain presenting to the Accident and Emergency department. Another limitation is that this study only assessed the potential benefit from a

single measurement of H-FABP at the time of admission. Sequential measurements were not investigated. Myoglobin was not measured for comparison purposes. Unlike myoglobin, the concentration of H-FABP in cardiac muscle is higher than in skeletal muscle.<sup>10</sup> This may mean that H-FABP is potentially more suitable than myoglobin as an early marker of myocyte injury. This study was designed taking cTnI done after 12 h of admission as a gold standard for diagnosis of AMI though it is not 100% specific.

#### 4.2. Conclusions

H-FABP is one of the promising new biomarkers for myocardial tissue injury detection. H-FABP is a highly sensitive biomarker for acute ischemia and infarction. Measurement of H-FABP in patients with acute ischemic-type chest pain at the time of admission will assist in the early diagnosis of AMI. For patients presenting within 6 h of symptom onset, the sensitivity of H-FABP is significantly higher than cTnI and CK-MB. Cardiac troponins are specific but rather late markers for detection of AMI. H-FABP as early marker and cTnI as late marker would be the ideal combination to cover the complete diagnostic window for AMI. However, the specificity of H-FABP alone for diagnosis of acute MI is poor. H-FABP elevation was also found in patients with chest pain and significant stenosis on CAG without myocardial infarction. This sensitive detection of myocardial ischemia by H-FABP may also be applied in patients with unstable angina though further studies are required. H-FABP can also be used as a marker for early detection of STEMI before the ECG changes become apparent.

#### Conflicts of interest

The authors have none to declare.

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# A Study on the Role of Heart Type Fatty Acid Binding Protein in the Diagnosis of Acute Myocardial Infarction

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## ABSTRACT

**Introduction:** Heart type Fatty Acid Binding Protein (H-FABP) has been proposed as an early cardiac biomarker for the diagnosis of acute myocardial Infarction (AMI) using animal models and clinical samples.

**Aim:** The study aimed to evaluate the role of H-FABP in early detection of AMI by comparing its sensitivity, specificity and predictive value with Creatinine Kinase-MB (CK-MB) and Cardiac Troponin I (cTnI).

**Materials and Methods:** This is a cross-sectional descriptive study of 50 patients admitted with the diagnosis of AMI at a tertiary care hospital in South India. The study group was categorised in to those coming to the hospital within four hours of symptom onset and those coming in between 4 to 12 hours. H-FABP was compared with those of troponin T and myoglobin tests.

**Results:** Among patients presenting within four hours of symptom onset, the sensitivity of H-FABP was 60% and was significantly

higher than that of cardiac Troponin I (cTnI, 18.8%) and Creatinine Kinase (CK)-MB (12.5%). But specificity was only 23.53% and was less than that of cTnI (66.67%) and CK-MB (100%). In patients presenting during 4 to 12 hours of symptom onset, the sensitivity of H-FABP was 86.96% which was comparable to that of cTnI (90.9%) and CK-MB (77.3%). The specificity was 60% in the 4-12 hours group which was comparable to that of cTnI (50%) and CK-MB (50%).

**Conclusion:** The H-FABP is a sensitive biomarker for the diagnosis of AMI in the initial hours after symptom onset when the standard biomarkers may not be elevated, but it is less specific. During 4-12 hours of symptom onset it is as sensitive and specific as standard cardiac biomarkers troponin and CK-MB. Due to these factors H-FABP can be considered as a promising cardiac biomarker which can be used along with troponins and CK-MB at present.

**Keywords:** Cardiac biomarkers, Cardiac Troponin I (cTnI), Creatinine kinase, Sensitivity, Specificity

## INTRODUCTION

Coronary heart disease which was earlier more common in developed countries is now common in developing countries including India [1]. Asian Indians have much higher incidence of Coronary Artery Disease (CAD) as compared to all other ethnic groups. CAD among Asian Indians has been found to be more severe, diffuse and associated with serious complications and increasing mortality at a younger age and its incidence has dramatically increased in recent years [2]. Heart type Fatty Acid Binding Protein (H-FABP) has been proposed as an early cardiac biomarker for the diagnosis of Acute Myocardial Infarction (AMI) using animal models [3,4] and clinical samples [5,6]. H-FABP is proved to be a sensitive early biomarker in Acute Coronary Syndrome (ACS) [7]. Rapid detection of H-FABP by immuno-testing has shown good sensitivity and negative predictive value compared to conventional methods in patients with AMI [8]. Some promising results were found in previous studies from India on H-FABP in patients with Acute Coronary Syndrome (ACS) [9-12]. Hence in this study the role of H-FABP in the diagnosis of AMI, particularly in the initial hours after symptom onset, is studied and compared with the established biomarkers Creatinine Kinase-MB (CK-MB) and troponin. The study was done with the following objectives: 1) To study the role of heart type fatty acid binding protein in the diagnosis of acute myocardial infarction; 2). To study the sensitivity, specificity and predictive value of H-FABP in the diagnosis of acute myocardial infarction and to compare with the CK-MB and cardiac Troponin I (cTnI).

## MATERIALS AND METHODS

This study was carried out at in a tertiary medical college hospital in South India during the period between November 2009 and October 2010. This study was Ethically approved by the Ethical committee of the institution.

This is a cross-sectional descriptive study involving 50 patients admitted to the Intensive Cardiac Care Unit (ICCU) with the diagnosis of acute myocardial infarction. AMI was defined as: typical anginal pain at rest lasting more than 20 minutes; previously diagnosed angina that has become more frequent, longer in duration, or more easily provoked. Typical electrocardiographic changes defined as:  $\geq 1$  mm ST-segment elevation in at least two anatomically contiguous limb leads,  $\geq 1$  mm ST-segment elevation in a precordial lead V4 through V6,  $\geq 2$  mm ST-segment elevation in V1 through V3, ST-segment depression by more than 0.05 mV in two or more contiguous leads, marked symmetrical T-wave inversion by more than 0.2 mV in the precordial leads, new bundle branch block, and/or sustained ventricular tachycardia [13]. Elevation of conventional cardiac enzymes included Troponin-I, and/or CK-MB. Presence of at least two positive factors (history, ECG changes as mentioned above and cardiac markers) constituted the diagnosis of ACS.

The patients were categorised in to those coming to the hospital within four hours of symptom onset and those coming in between 4 to 12 hours. Patients with cerebrovascular accident, known renal disease and those coming after 12 hours of symptom onset were excluded from the study. Applying these criteria, 50 eligible patients were selected with random sampling and included in the study after informed consent.

A detailed history was taken and clinical examination was done in all the patients with particular reference to the cardiovascular system. History included age, gender, family history of hypertension, diabetes, Ischemic Heart Disease (father/mother/siblings), history of smoking and tobacco use. Body Mass Index (BMI) was calculated using the formula BMI=Weight (kg)/(Height in metre)<sup>2</sup> and were categorised as normal: 8.5 - 22.9 kg / m<sup>2</sup>, overweight: 23- 24.9 kg / m<sup>2</sup> and obese:  $\geq 25$  kg / m<sup>2</sup>. Blood sugar was estimated by Trinder's (Glucose oxidase) method and read at 505/670 nm. Total

cholesterol and triglycerides were measured using Trinder's method. Total cholesterol <200mg/dl was taken as normal and triglycerides <150mg/dl was taken as normal.

Standard 12 lead ECG was taken for all the patients. CK-MB was estimated using immuno-inhibition method. Values <25 IU/L was considered as normal. Two dimensional echocardiography was done for all the patients included in this study. Treatment given, complications and the course in the hospital were recorded.

### Estimation of Troponin I and H-FABP

Estimation was done using Cardio-detect qualitative immunological rapid test combi kit. The test field for both troponin I and H-FABP was filled with 3 to 4 drops of whole blood, serum or plasma. The result is read after 15 minutes. If both the test (T) and control (C) lines were seen then it was taken as positive result. If only control (C) is seen then it is taken as negative result. If no line is seen then it was taken as invalid result.

### The Test Principle

H-FABP: The test contains two different monoclonal antibodies specific for H-FABP, of which one is gold-labelled. The sample liquid releases the gold-labelled anti-FABP antibody from its matrix. This antibody forms an intermediary complex with the FABP present in the sample. This complex spreads across the test strip up to the position marked by 'T' where a second antibody is located. The intermediary complex and the second antibody form a sandwich complex showing up as a red line. A sample without H-FABP does not form a sandwich complex and therefore, forms no red line [14].

cTnI: If the sample contains cTnI, it interacts with anti cTnI antibodies and particles coated with the bio-tynilised anti cTnI antibodies. This complex passes over the test strip up to the position marked with 'T' where a line is coated with Streptavidin. The complex reacts with the Streptavidin showing up as a red line. A sample without cTnI forms no red line [14].

### Evaluation of the Test

For H-FABP: If two lines seen (at 'C' and 'T') - Positive (H-FABP>7ng/ml), if only one line at 'C' - Negative (H-FABP<7ng/ml), no line or one line at 'T' only- Invalid test. For cTnI: If two lines seen (at 'C' and 'T') - Positive (cTnI>1ng/ml), if only one line at 'C' - Negative (cTnI<1ng/ml), no line or one line at 'T' only- Invalid test.

### STATISTICAL ANALYSIS

Data was entered in Microsoft excel spread sheet and analysed statistically using SPSS software version 17. Results were considered significant if the p-value was below 0.05. Chi – square test and Pearson's correlation test was done for statistical analysis.

### RESULTS

A total of 50 patients were selected for the study. They were divided into two groups those presenting within four hours after the symptom onset and those presenting during 4-12 hours. Out of 50 patients, 22 presented within four hours (44%) and 28 patients presented during 4-12 hours (56%). There was no statistical difference between males and females with regard to time window of presentation to hospital after symptom onset.

Thirty nine patients were males (78%) and 11 were females (22%). Six patients were aged <40 years (12%), 15 were in 40-50 years age group (30%), 17 in 50-60 years age group (34%) and 12 were aged >60 years (24%). The mean age group among H-FABP positive patients was  $51.92 \pm 9.437$  years and  $55.92 \pm 9.931$  among H-FABP negative patients. H-FABP was positive among 20 alcoholics (90.9%) and 18 non-alcoholics (64.3%) [Table/Fig-1].

Thirty two males and six females were positive for H-FABP (82.05% v/s 54.55%). There was statistically significant correlation between

ECG changes and echocardiographic findings and the group which received thrombolysis with H-FABP positivity (p-value 0.000) [Table/Fig-2].

In this study, among patients presenting within four hours of symptom onset, the sensitivity of H-FABP was 60% and was significantly higher than that of cTnI (18.8%) and CK-MB (12.5%). But specificity was only 23.53% in the initial four hours which was less than that of cTnI (66.67%) and CK-MB (100%). In patients presenting during 4 to 12 hours of symptom onset, the sensitivity of H-FABP was 86.96% which was comparable to that of cTnI (90.9%) and CK-MB (77.3%). The specificity was 60% in the 4-12 hours group which was comparable to that of cTnI (50%) and CK-MB (50%). Overall diagnostic accuracy compared to troponin was 60% and compared to CK-MB was 56% [Table/Fig-3,4].

Patient characteristics		H-FABP				p-value*	
		Positive		Negative			
		N	%	N	%		
Gender	Male	32	64	7	14	0.06	
	Female	6	12	5	10		
Age group (in years)	<40	5	10	1	2	0.3	
	40 - 50	11	22	4	8		
	50 - 60	15	30	2	4		
	>60	7	14	5	10		
Body Mass Index	Normal	23	46	10	20	0.15	
	Increased	15	30	2	4		
Presence of hypertension	Yes	17	34	5	10	0.85	
	No	21	42	7	14		
Presence of diabetes mellitus	Yes	9	18	6	12	0.08	
	No	29	58	6	12		
History of smoking	Smoker	30	60	6	12	0.05	
	Non-smoker	8	16	6	12		
History of alcohol consumption	Yes	20	40	2	4	0.03	
	No	18	36	10	20		
Outcome	Improved	35	70	12	24	0.32	
	Expired	3	6	0	0		

[Table/Fig-1]: Distribution of H-FABP with respect to study characteristics (N=50). \*Statistical significance was considered at  $p \leq 0.05$ .

Variables		H-FABP				p-value*	
		Positive		Negative			
		N	%	N	%		
Killip class	I	17	34	6	12	0.58	
	II	9	18	6	12		
	III	2	4	0	0		
	IV	10	20	0	0		
Triglyceride levels	Normal	7	14	4	8	0.28	
	Increased	31	62	8	16		
Cholesterol levels	Normal	3	6	2	4	0.38	
	Increased	35	70	10	20		
Electrocardiograph findings	ST segment elevation	26	52	3	6	<0.001	
	Other changes	12	24	2	4		
	No changes	0	0	7	14		
Echocardiograph findings	RWMA	32	64	3	6	<0.001	
	No RWMA	6	12	9	18		
Thrombolysis	Done	25	50	3	6	0.013	
	Not done	13	26	9	18		

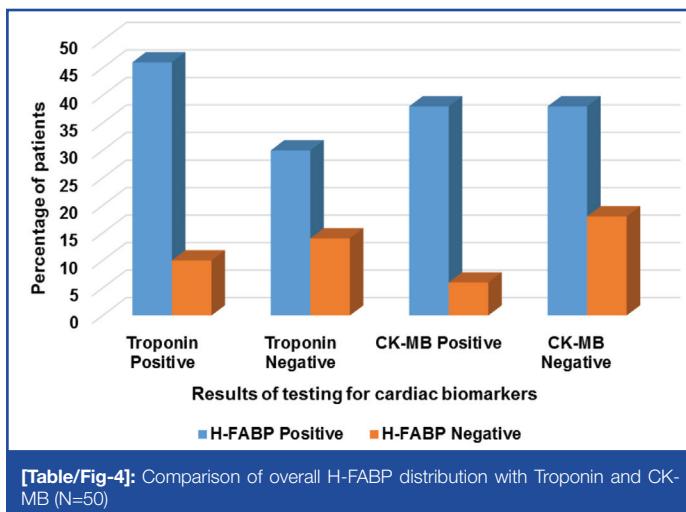
[Table/Fig-2]: Distribution of H-FABP among patients with respect to their Killip class, laboratory parameters and thrombolysis (N=50).

\*Statistical significance was considered at  $p \leq 0.05$ . RWMA – Regional wall motion abnormality.

H-FABP		Troponin		CK-MB	
		Positive N (%)	Negative N (%)	Positive N (%)	Negative N (%)
0 - 4 hrs	Positive	3 (6)	13 (26)	2 (4)	14 (28)
	Negative	2 (4)	4 (8)	0 (0)	6 (12)
4 – 12 hrs	Positive	20 (40)	2 (4)	17 (34)	5 (10)
	Negative	3 (6)	3 (6)	3 (6)	3 (6)
Overall	Positive	23 (46)*	15 (30)*	19 (38)†	19 (38)†
	Negative	5 (10)*	7 (14)*	3 (6)†	9 (18)†

[Table/Fig-3]: Comparison of H-FABP distribution with Troponin and CK-MB.

\*Sensitivity = 82.14%, Specificity= 31.82%, Positive Predictive Value=60.53%, Negative Predictive Value=58.33%, Diagnostic Accuracy= 60%. †Sensitivity = 86.36%, Specificity= 32.14%, Positive Predictive Value=50%, Negative Predictive Value=75%, Diagnostic Accuracy= 56%.



[Table/Fig-4]: Comparison of overall H-FABP distribution with Troponin and CK-MB (N=50)

## DISCUSSION

Early diagnosis and treatment is very important in preserving the myocardium and in limiting the ischaemic damage. Studies have shown that the serum levels of gold standard cardiac biomarkers start to rise relatively late (3-4 hours in case of cardiac troponins and 4-6 hours in case of CK-MB) and myoglobin which can be detected early is nonspecific to myocardium. Studies also have shown that non-diagnostic ECGs are recorded in approximately half of the patients presenting to emergency department with chest pain who ultimately are shown to have AMI. Hence an early biomarker is essential for the accurate diagnosis of AMI. Heart Type Fatty Acid Binding Protein (H-FABP) has shown promise in this regard in various studies.

The present study aimed at evaluating the role of H-FABP in the diagnosis of AMI and also to compare it with the standard biomarkers troponin and CK-MB. It also aimed at finding out the distribution of H-FABP with regard to variables like age and sex of the patient, BMI, lipid levels, smoking, and alcoholism and in those with systemic hypertension and diabetes mellitus. It also aimed at correlating the H-FABP positivity with ECG and echocardiographic findings.

This observation is supported by some of the following studies. According to a study by Okamoto et al., the overall sensitivity within 12 hours of symptom onset was 92.9% for H-FABP, 88.6% for myoglobin and 18.6% for CK-MB [9]. The overall specificity was 67.3% for H-FABP, 57.1% for myoglobin and 98.0% for CK-MB. A study from Chennai showed H-FABP to be a good discriminator between patients with and without IHD [15]. It also showed that troponin levels rise more than six hours after symptom onset, H-FABP is usually positive within first four hours. At the optimum cut-off value (17.7 ng/ml), the sensitivity and specificity were found to be 87% and 93% respectively.

In another study, among patients presenting within four hours of symptom onset, sensitivity of H-FABP was higher than cTnT (73%

v/s 53%). Specificity of H-FABP was 71% [16]. Combined use of H-FABP and cTnT significantly improved the sensitivities of both to 85%. In a study by Umut Cavus et al., H-FABP had sensitivity equal to that of CK-MB and superior to that of myoglobin (97.6% v/s 96.7% v/s 85.4%) in initial 4 hours [17].

In a study by Ecollan P et al., a positive H-FABP using cardio-detect assay had a significantly better sensitivity than cTnI, myoglobin and CK-MB (87.3% v/s 21.8%, 64.2% and 41.5% respectively) [18]. A study by Ruzgar et al., showed sensitivity of 38% with troponin, 76% with CK-MB and 95% with H-FABP in patients admitted within 6 hours of chest pain onset [19]. In another study conducted by Mad P et al., in 280 patients presenting to the hospital with a median time of three hours of symptom onset, H-FABP had a sensitivity of 69% and specificity of 74% and AMI was diagnosed significantly earlier than by troponin [20].

In this study, H-FABP was found to be more sensitive but less specific compared to cardiac troponin I and CK-MB during the initial four hours of symptom onset [Table/Fig 4]. During the 4-12 hours of symptom onset, H-FABP showed similar sensitivity and specificity compared to cardiac troponin I and CK-MB. It did not show any significant difference between males and females, different age groups, diabetics and non- diabetics, hypertensives and normotensives, smokers and non-smokers and between those having hyperlipidaemia and normolipidaemia.

## LIMITATION

The main limitation of the study was the small sample size. The sample size calculation and the required numbers are not accomplished because of feasibility constraints due to the cost of the kits and this may affect the analysis of study results. Each patient was tested only once and serial evaluation of the biomarkers was not done. Also, quantitative assay for troponin and H-FABP was not performed. Also, cardiac Troponin T and myoglobin were not measured.

## CONCLUSION

The heart type fatty acid binding protein is a sensitive biomarker for the diagnosis of acute myocardial infarction in the 4-12 hours of symptom onset when the standard biomarkers may not be elevated, but it is less specific. The H-FABP assay is not influenced by the age, sex, BP, glycaemic status, BMI and lipid levels of the patient. Due to these factors H-FABP can be considered as a promising cardiac biomarker which can be used along with troponins and CK-MB at present.

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# Heart-type fatty acid binding protein is a sensitive biomarker for early AMI detection in troponin negative patients: a pilot study

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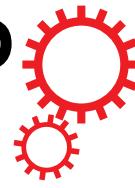
## Abstract

**Background:** Early detecting AMI in individuals presenting to the ED with chest pain continues to be a challenge. cTn is the gold standard for AMI diagnosis but early presenters (<1 hours from symptom onset) maybe cTn negative on admission. We analysed the diagnostic value of h-FABP and hs-Tnl in patients presenting to ED with chest pain and no cTnl elevations.

**Methods:** 28 AMI and 28 no-AMI individuals both presented to ED within one hour from pain onset were included. Blood donors were analysed for h-FABP cut-off identification. Among AMI patients, 55% were positive for h-FABP and 34.6% were positive for hs-Tnl ( $p = .015$ ), thus 21% were positive only for h-FABP. The diagnostic accuracy was assessed by ROC curve. h-FABP showed a higher sensitivity but lower specificity than hs-Tnl.

**Conclusions:** In our study, the frequency of h-FABP positivity among AMI patients was higher than that of hs-Tnl, which would have missed six of them; however, hs-Tnl AUC was superior to that of h-FABP. These preliminary findings might confirm that h-FABP may be a good candidate for AMI rule-in/rule-out within the ED context.

# SCIENTIFIC REPORTS



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## The prognostic significance of heart-type fatty acid binding protein in patients with stable coronary heart disease

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To investigate the prognostic value of heart-type fatty acid binding protein (H-FABP) in patients with stable coronary heart disease (SCHD). A total of 1,071 patients with SCHD were prospectively enrolled in this Taiwan multicenter registry study, followed for 24 months. The cut-off value of H-FABP, 4.143 ng/mL, was determined using receiver operating characteristic curves. The primary cardiovascular (CV) outcome was composite CV events, defined as cardiovascular or cerebrovascular death, myocardial infarction (MI), stroke, angina related-hospitalization, PAOD-related hospitalization and heart failure. Secondary outcomes included CV or cerebrovascular death, nonfatal MI, nonfatal stroke, and acute heart failure-related hospitalization. We found that the high H-FABP group had more than a two-fold higher rate of primary CV outcomes than the low H-FABP group (32.36% vs. 15.78%,  $p < 0.001$ ). Eleven patients (4.82%) of the high H-FABP group died during the 24 months of follow-up, compared to only one patient (0.12%) in the low H-FABP group. The acute heart failure-related hospitalization rate was also significantly higher in the high H-FABP group (3.5% vs. 0.95%,  $p < 0.005$ ). The results remained significant after adjusting for baseline covariates. In conclusion, H-FABP was an independent predictor for CV outcomes in the patients with SCHD, mainly in CV death and acute heart failure-related hospitalization.

Ischemic heart disease and stroke have been the leading causes of death globally in the past decades, and the mortality rate from these diseases is gradually increasing. In addition to traditional cardiovascular (CV) risk factors such as smoking, type 2 diabetes mellitus (T2DM), hypertension (HTN) and dyslipidemia, researchers have investigated potential novel biomarkers, for instance, copeptin<sup>1</sup>, pentraxin-3<sup>2</sup> and heart-type fatty acid binding protein (H-FABP) to predict the clinical course and CV outcomes. In particular, H-FABP has been widely studied

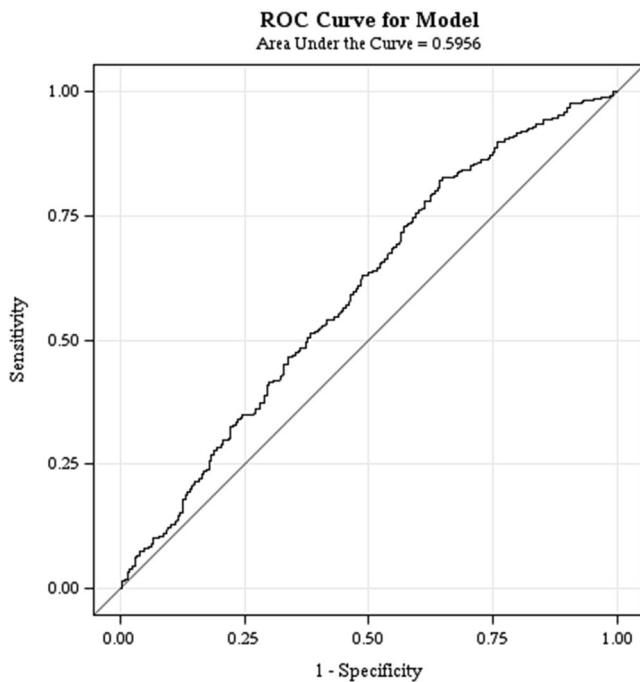
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Events	Number of case (%)
Total CV events	207
CV or cerebrovascular death	12 (5.8%)
Nonfatal myocardial infarction	24 (12%)
Nonfatal stroke	6 (3%)
Angina-related hospitalization	132 (64%)
PAOD-related hospitalization	14 (7%)
Heart failure	19 (9.2%)
Acute heart failure-related hospitalization	16 (7.7%)
Aortic dissection	1 (0.5%)
Brady- or tachyarrhythmia	2 (1%)

**Table 1.** Cardiovascular Events in 24 months. CV = cardiovascular, MI = myocardial infarction, PAOD = peripheral arterial occlusive disease.



**Figure 1.** Receiver operating characteristic curve (ROC) analysis plot with area under the curve, sensitivity and specificity of H-FABP in prediction of total cardiovascular events.

in patients with acute coronary syndrome (ACS), and it has been suggested to increase diagnostic sensitivity and possibly predict long-term survival<sup>3</sup>.

H-FABP is a human protein that is encoded by the fatty acid binding protein 3 (FABP3) gene and is located on chromosome 1p32-p35. It is a cytoplasmic protein which was first isolated from ischemic rat hearts in 1988, and was identified as being released from injured myocardium<sup>4,5</sup>. Associations between H-FABP and ACS<sup>6-8</sup>, acute kidney injury<sup>9</sup>, post-cardiac surgery<sup>10</sup>, acute pulmonary embolism<sup>11</sup>, acute ischemic stroke<sup>12</sup>, severe sepsis<sup>13</sup>, acute heart failure<sup>14</sup>, hypothyroidism<sup>15</sup> and hyperthyroidism<sup>16</sup> have been reported over the past decades. On the other hand, H-FABP has also been used to assess perioperative cardiac risk<sup>17,18</sup>. However, the prognostic implication of H-FABP in patients with stable coronary heart disease (SCHD) is unknown. The aim of this study was to investigate the prognostic value of H-FABP in CV outcomes in patients with SCHD.

## Results

**Patients.** A total of 1,072 SCHD patients from the National Taiwan Biosignature Research (NTBR) cohort study were enrolled and followed for 24 months or until a CV event. At 24 months, 207 cardiovascular events had occurred, including 12 CV deaths, 24 nonfatal myocardial infarction (MI), 6 nonfatal strokes and 16 acute heart failure-related hospitalizations (Table 1).

The cut-off value of H-FABP (4.143 ng/mL) was determined by receiver operating characteristic curves (ROC) curve analysis (Fig. 1) between the patients with and without CV events from the blood sample obtained at enrollment. The baseline characteristics revealed that the patients with a high level of H-FABP had higher rates of HTN, but lower rate of family history of premature coronary artery disease (CAD). Except for a lower level of serum

	Total n	(%)	H-FABP < 4.143 ng/mL		H-FABP ≥ 4.143 ng/mL		<i>p</i>
			n	(%)	n	(%)	
Male gender	1071	913 (85.25%)	843	718 (85.17%)	228	195 (85.53%)	0.894
Hypertension	1071	698 (65.17%)	843	531 (62.99%)	228	167 (73.25%)	0.004
Diabetes	1071	408 (38.1%)	843	283 (33.57%)	228	125 (54.82%)	<0.001
Smoking	1071	603 (56.3%)	843	482 (57.18%)	228	121 (53.07%)	0.267
Family history of premature CAD	1071	246 (22.97%)	843	213 (25.27%)	228	33 (14.47%)	0.001
Previous stroke	1071	28 (2.61%)	843	22 (2.61%)	228	6 (2.63%)	0.985
1-vessel disease	1071	596 (55.65%)	843	482 (57.18%)	228	114 (50%)	0.138
2-vessel disease	1071	165 (15.41%)	843	124 (14.71%)	228	41 (17.98%)	0.118
3-vessel disease	1071	21 (1.96%)	843	16 (1.9%)	228	5 (2.19%)	0.699
		Median (IQRs)		Median (IQRs)		Median (IQRs)	
Age, year	1071	64.9 (57.2–74.3)	843	63.3 (56.5–71.6)	228	72.5 (62.2–81.0)	<0.001
BMI (kg/m <sup>2</sup> )	1070	25.9 (23.7–28.3)	842	26.0 (23.7–28.4)	228	25.6 (23.4–28.4)	0.555
Systolic BP, mmHg	1071	130 (119–114)	843	130 (119–140)	228	131 (120–147)	0.016
Diastolic BP, mmHg	1071	74 (66–83)	843	75 (67–83)	228	73 (65–83)	0.112
Glucose, mg/dL	1065	106 (95–131)	839	105 (94–126)	226	114 (97–143)	0.002
Hemoglobin, g/dL	1019	13.6 (12.4–14.9)	796	14.0 (12.8–15.1)	223	12.4 (11.0–13.7)	<0.001
LDL-C, mg/dL	1066	90 (73–111)	841	90 (74–112)	225	91 (72–108)	0.322
HDL-C, mg/dL	1065	40 (35–48)	840	41 (35–48)	225	38 (33–45)	0.007
Serum creatinine, mg/dL	1066	1.03 (0.87–1.28)	839	0.98 (0.83–1.14)	227	1.50 (1.19–2.36)	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	1066	74 (59–90)	839	79 (66–95)	227	68 (28–63)	<0.001
hs-CRP, mg/dL	779	0.14 (0.07–0.31)	611	0.13 (0.07–0.27)	168	0.22 (0.10–0.58)	0.004
NT-pro BNP, pg/mL	1071	171 (66–460)	843	141 (58–367)	228	334 (109–880)	0.001

**Table 2.** Baseline characteristics of patients with stable coronary heart disease. Results are expressed as percentage or medians (IQRs). BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein -cholesterol; LDL-C = low-density lipoprotein-cholesterol; hs-CRP = high sensitivity C-reactive protein; NT-pro BNP = N-terminal pro-brain natriuretic peptide.

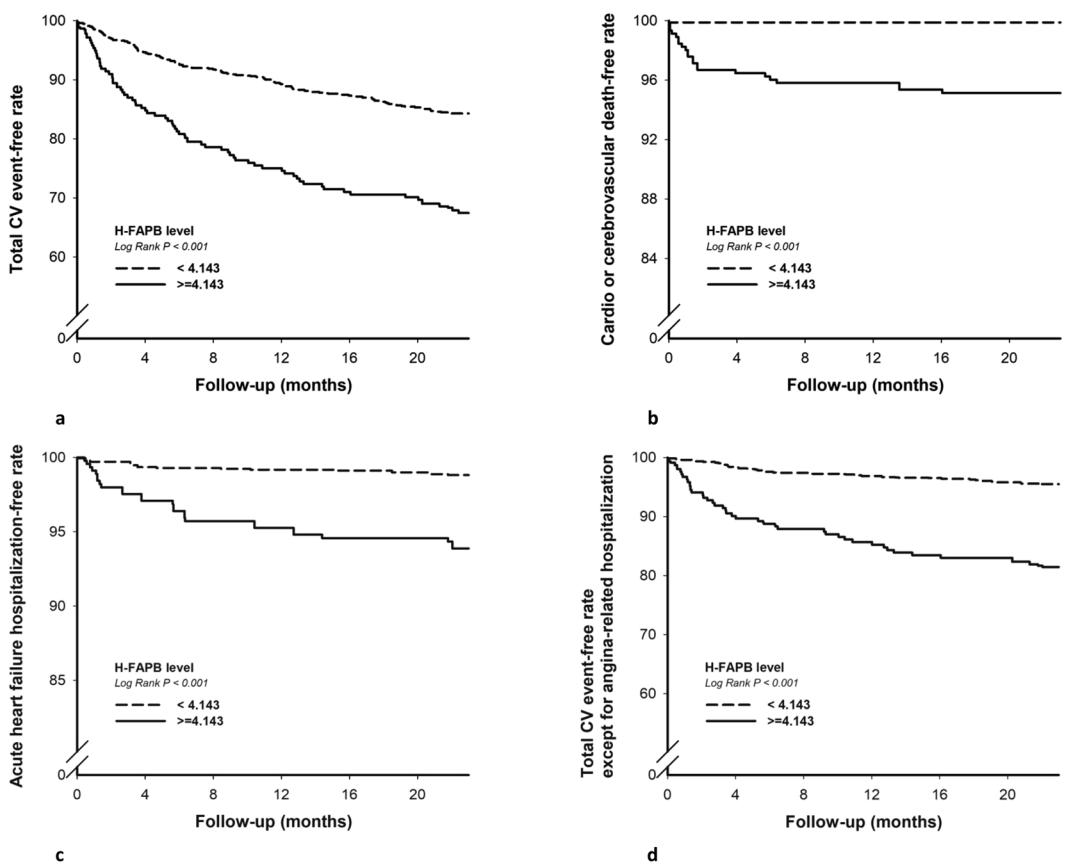
	All (n = 1,071)	H-FABP < 4.143 ng/mL, (n = 843)	H-FABP ≥ 4.143 ng/mL, (n = 228)	<i>p</i>
<b>Primary outcome</b>				
Total CV events, n (%)	207 (19.33%)	133 (15.78%)	74 (32.46%)	<0.001
<b>Secondary outcome</b>				
CV or cerebrovascular death, n (%)	12 (1.12%)	1 (0.12%)	11 (4.82%)	<0.001
Nonfatal myocardial infarction, n (%)	24 (2.24%)	16 (1.9%)	8 (3.51%)	0.145
Nonfatal stroke, n (%)	6 (0.56%)	3 (0.36%)	3 (1.32%)	0.085
Acute heart failure-related hospitalization, n (%)	16 (1.49%)	8 (0.95%)	8 (3.51%)	0.005
Total CV events except for angina-related hospitalization, n (%)	80 (7.47%)	38 (4.51%)	42 (18.00%)	<0.001

**Table 3.** Clinical outcomes in 24 months. CV = cardiovascular.

high-density lipoprotein cholesterol (HDL-C), patients with a high level of H-FABP had significantly higher blood glucose, systolic blood pressure (SBP), serum creatinine, high sensitivity C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) than those with a low level of H-FABP (Table 2).

**Primary outcomes.** After 24 months of follow up, the high H-FABP group had more than a two-fold higher rate of primary CV events than the low H-FABP group (32.36% vs. 15.78%, *p* < 0.001) (Table 3). The Kaplan-Meier curves of the two groups were significantly separated from the beginning of the study to 24 months (Fig. 2a).

**Secondary outcomes.** A total of 11 deaths (4.82%) occurred in the high H-FABP group, compared with only one (0.12%) in the low H-FABP group (Table 3 and Fig. 2b). In addition, the high H-FABP group had a significantly higher rate of acute heart failure-related hospitalizations (3.5%) compared to the low H-FABP group (0.95%) (Table 3 and Fig. 2c). Although statistically non-significant, there was also a trend of higher rate of non-fatal MI and nonfatal stroke in the high H-FABP group (Table 3). There were 80 patients with total CV events except for “angina-related hospitalization”, 38 patients in H-FABP group, 42 patients in H-FABP group (4.51% vs 32.46%, *p* < 0.001). The difference between these two groups remained significant (Fig. 2d).



**Figure 2.** Kaplan–Meier survival curves analysis showing total cardiovascular (CV) event-free rate (a), CV or cerebrovascular death-free rate (b), acute heart failure hospitalization-free rate (c), and total CV event-free rate except for angina-related hospitalization (d) in patients with serum H-FABP  $\geq 4.143$  ng/mL and H-FABP  $< 4.143$  ng/mL (all  $p < 0.001$ ).

In multivariate Cox proportional hazards analysis adjusted for age, sex, body mass index (BMI), serum creatinine, estimated glomerular filtration rate (eGFR), HDL-C, hemoglobin (Hb), blood glucose, hs-CRP, NT-proBNP, SBP, smoking, family history of premature CAD, history of hypertension and diabetes mellitus, high H-FABP level was still an independent prognostic risk factor for CV events (HR 2.93, 95% CI 1.95–4.394,  $p < 0.001$ ). In addition, a high level of H-FABP also predicted CV death (HR 22.89, 95% CI 2.16–242.55,  $p = 0.009$ ) and acute heart failure-related hospitalizations (HR 5.16, 95% CI 1.096–24.324,  $p = 0.038$ ) in the 24-month follow-up period, even after adjusted for other covariates (Table 4).

## Discussion

This study is the first prospective cohort study to demonstrate that a higher serum H-FABP level ( $\geq 4.143$  ng/mL) is an independent predictor for CV events, particularly for cardio- and cerebrovascular death and acute heart failure-related hospitalizations in patients with SCHD. Our result was concordant with the Takahata study<sup>19</sup>, which also found that H-FABP level was increased in association with greater numbers of cardiovascular risk factors. In addition, Takahata study noted higher H-FABP level was an independent risk factor for all-cause and cardiovascular deaths in 3,503 subjects who participated in a community-based health checkup in a 7-year follow-up.

The early diagnosis of acute MI is still challenging for emergency physicians despite the wide application of myoglobin and high-sensitivity cardiac troponin (cTn) in emergency rooms, because the elevation of most myocardial injury serum markers are delayed by at least 2–4 hours after an ischemic insult. In 2000, an experimental study of ligation of the left main coronary artery in mice demonstrated that the concentration of H-FABP at 4 hours could be used to stratify MI compared to cTn at 48 hours<sup>20</sup>. In addition, Okamoto *et al.* reported that H-FABP is more sensitive than myoglobin and creatinine kinase isoenzyme MB for the diagnosis of acute MI in the early phase<sup>21</sup>. In 2006, O'Donoghue *et al.* reported an association between an elevated level of H-FABP and increased risks of death and major cardiac events in patients with ACS<sup>22</sup>. Collinson *et al.*<sup>23</sup> compared the diagnostic performances of cTn-I, H-FABP and copeptin in low-risk patients presenting with chest pain. The authors concluded that cTn-I remained the best single test, with the incremental diagnostic sensitivity of serum H-FABP, but not copeptin. Furthermore, a recent dobutamine stress echocardiography (DSE) study reported significantly increased levels of serum H-FABP at 1 hour in the presence of DSE-induced ischemia, in contrast to DSE negative group, whose serum H-FABP remained unchanged before and 1 hour after the test<sup>24</sup>. However, in a study that was

	Univariate*		Multivariate**	
	HR (95% CI)	p	HR (95% CI)	p
<b>Primary outcome</b>				
Total CV events	2.35 (1.77–3.13)	<0.001	2.93 (1.95–4.39)	<0.001
<b>Secondary outcome</b>				
CV or cerebrovascular death	41.75 (5.39–323386)	0.004	22.89 (2.16–242.55)	0.009
Nonfatal myocardial infarction	1.96 (0.84–4.58)	0.120	2.62 (0.80–8.59)	0.112
Nonfatal stroke	3.91 (0.79–19.35)	0.085	1.56 (0.06–38.62)	0.786
Acute heart failure related hospitalization	3.90 (1.46–10.39)	0.007	5.16 (1.10–24.32)	0.038

**Table 4.** Univariate and multivariable logistic Cox-proportional regression analysis models for clinical outcomes. CV = cardiovascular. \*Non-adjusting. \*\*Adjusting for significant variables in univariate analysis, which including age, gender, body mass index, serum creatinine, estimated glomerular filtration rate, high-density lipoprotein, low-density lipoprotein, hemoglobin, fasting glucose, high sensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide, systolic blood pressure, history of hypertension, smoking and diabetes, family history of premature CAD.

expected H-FABP to increase during exercise stress testing (EST), serum H-FABP tended to decline statistically significant from the basal level to 3 hours after the EST<sup>25</sup>. A recent systemic review of H-FABP in ACS found marked heterogeneity in the prognostic impact of H-FABP between studies, reflecting differences in sampling times and the population at risk. Hence, it may not be possible to routinely use H-FABP as a prognostic marker in patients with suspected ACS<sup>26</sup>.

Wunderlich *et al.* were the first to report that an early elevation of serum H-FABP and brain type fatty acid binding protein (B-FABP) concentration were significantly associated with the severity of neurological deficits and functional outcomes in patients after an acute ischemic stroke<sup>12</sup>. The peak levels of H-FABP and B-FABP occur 2 to 3 hours after an event and remain elevated for up to 120 hours. In addition, a high level of H-FABP is associated with large infarctions on brain computed tomography. Another investigation of 41 patients with acute stroke (31 with ischemic stroke, 10 with intracerebral hemorrhage) demonstrated that serum H-FABP and ischemic-modified albumin (IMA) levels increased within 4.5 hours<sup>27</sup>. Nonetheless, An *et al.* reported that H-FABP was not an independent marker in patients with ischemic stroke, and thus that its clinical usefulness is limited<sup>28</sup>. In the current study, we demonstrated the prognostic value of H-FABP in CV events in patients with SCHD after successful treatment, but that it had limited value in the prediction of nonfatal MI and ischemic stroke. In this study, although statistically non-significant, there was also a trend of higher rate of nonfatal MI and nonfatal stroke in the high H-FABP group.

The relationship between H-FABP and heart failure was first reported in the early 2000s, when the concentration of H-FABP was positively correlated with the concentration of BNP in patients with acute deterioration of heart failure<sup>29</sup>. Later, Setsuka *et al.*<sup>30</sup> reported that H-FABP was present in the activation of tumor necrosis factor (TNF) and the Fas ligand system. This suggested a pathophysiological role of cardiomyocyte necrosis and/or apoptosis in patients with worsening heart failure. Moreover, Hoffmann *et al.*<sup>14</sup> investigated H-FABP in acute heart failure, and found that additional H-FABP measurements improved the diagnostic specificity and positive predictive value of NT-proBNP tests. In addition, their patients in the highest H-FABP quartile had significantly higher rates of all-cause mortality (HR 2.1–2.5; *p* = 0.04) and risk of re-hospitalization for acute heart failure at 5 years (HR 2.8–8.3, *p* = 0.001). Our study also demonstrated that the SCHD patients with high H-FABP level had a higher risk for acute heart failure-related hospitalizations at 24 months.

There are several limitations of this study. First, even though the criteria for patient enrollment and the protocol for clinical follow-up were clearly defined, selection bias arising from clinical profiles, investigator participation and treatment adherence by the patients could not be completely excluded<sup>31</sup>. Second, this is a hospital based rather than a community-based study, and this design was potentially limited by geographic variations such as environmental exposure to risk factors of CV disease<sup>32</sup>. Third, all the patients were stable during enrollment and followed up regularly for clinical events in the out-patient clinics of the medical centers. Their medications may have been adjusted by the specific cardiologists during follow-up. Thus, the potential effects of different cardiovascular drugs on clinical outcomes could not be well addressed<sup>33</sup>. Fourth, the very few cases of the each secondary event category, insufficient statistical power of predictive value of H-FABP could be derived from the multivariate analyses.

In conclusion, H-FABP was an independent predictor for total CV events in the patients with SCHD at 24 months, mainly for CV and cerebrovascular deaths and acute heart failure-related hospitalization.

## Methods

**Study population.** This NTBR was a prospective cohort study of patients with SCHD (aged  $\geq 20$  years) from nine medical centers in Taiwan<sup>31</sup>. At enrollment, all of the participants had undergone a percutaneous coronary intervention at least once and had been stable on medical treatment for at least 1 month. The exclusion criteria included hospitalization for any CV event within 3 months, and those unable or unwilling to be followed up during the following 1 year period. Specific clinical outcomes including all-cause, cardiovascular, cerebrovascular mortalities, and CV-related hospitalizations were confirmed using the Health and Welfare Data Science Center (HWDC) of Taiwan.

This study complied with the Declaration of Helsinki and was approved by the appropriate Health Authorities, independent Ethics Committees, and Institutional Review Boards (IRB) in each hospital as well as the Joint IRB

Ethics Committee Review Board in Taiwan. All of the patients agreed to participate and signed the informed consent form.

**Baseline clinical and biomarker data collection.** After enrollment, data were prospectively collected by physicians and nurses whenever feasible. Baseline characteristics included sex, age, HTN, T2DM, hyperlipidemia, smoking, family history of premature CAD, BMI, number of stenotic coronary arteries, and biochemical data including renal function, lipid profile at enrollment in each hospital were recorded. Hs-CRP was performed automatically with chemiluminescent immunoassay methods, on a Beckman Coulter DXC 800 immunoassay platform (Beckman Coulter, Inc. CA, USA). NT-pro BNP and H-FABP were measured manually on EMD Millipore's MILLIPLEX MAP Human CVD 1 Magnetic Bead kit (Millipore, Inc. MO, USA).

**Clinical follow-up.** Questionnaire and blood samples were obtained from the patients every 3 months in the first year and every 6 months thereafter for a total of 24 months. The primary CV outcome was composite CV events, defined as cardiovascular or cerebrovascular death, MI, stroke, angina-related hospitalization, PAOD-related hospitalization and heart failure. Heart failure was a composite of acute heart failure-related hospitalization, syncope, cardiopulmonary resuscitation, bradyarrhythmia, supraventricular tachyarrhythmia, ventricular arrhythmia, permanent pacemaker implantation and aortic dissection. The secondary outcomes included CV or cerebrovascular death, nonfatal MI, nonfatal stroke, and acute heart failure-related hospitalization.

**Statistical analysis.** The cut-off value of H-FABP was determined using ROC curve analysis between the patients with and without CV events from the blood sample obtained at enrollment. Baseline characteristics and CV outcomes were compared between the patients with high and low levels of H-FABP.

Results are expressed as median (interquartile ranges [IQRs]) for continuous variables, and qualitative variables are expressed in absolute frequencies (number of patients) and relative frequencies (percentage). Comparisons of continuous variables between groups were performed using ANOVA or Mann-Whitney *U* tests. The primary and secondary outcomes were described as overall percentages and expressed as means of proportions with a 95% confidence interval (CI). The Kaplan-Meier method was used to calculate events and survival rates. Hazard ratios (HRs) for the regression of Cox proportional hazards were used, along with the corresponding standard error, 95% CI, and *p* value. Independent baseline variables with a *p* value < 0.05 in the univariate analysis were included in the multivariate analysis. In all the tests, the two-tailed alpha significance level was 0.05. In addition, *p* values were reported up to three decimals, while those below 0.001 were reported as *p* < 0.001.

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## Author Contributions

S.K.H., Y.-W.W. and C.-C.W. conceived and designed the research. Y.-W.W., W.-K.T., H.-B.L., W.-H.Y., T.-H.L., H.-I.Y., K.-C.C., J.-H.W., J.-W.C. and C.-C.W. managed data collection. S.K.H. drafted the manuscript and designed the figures and tables. Y.-W.W. and C.-C.W. made critical revision of the manuscript. All authors reviewed the manuscript.

## Additional Information

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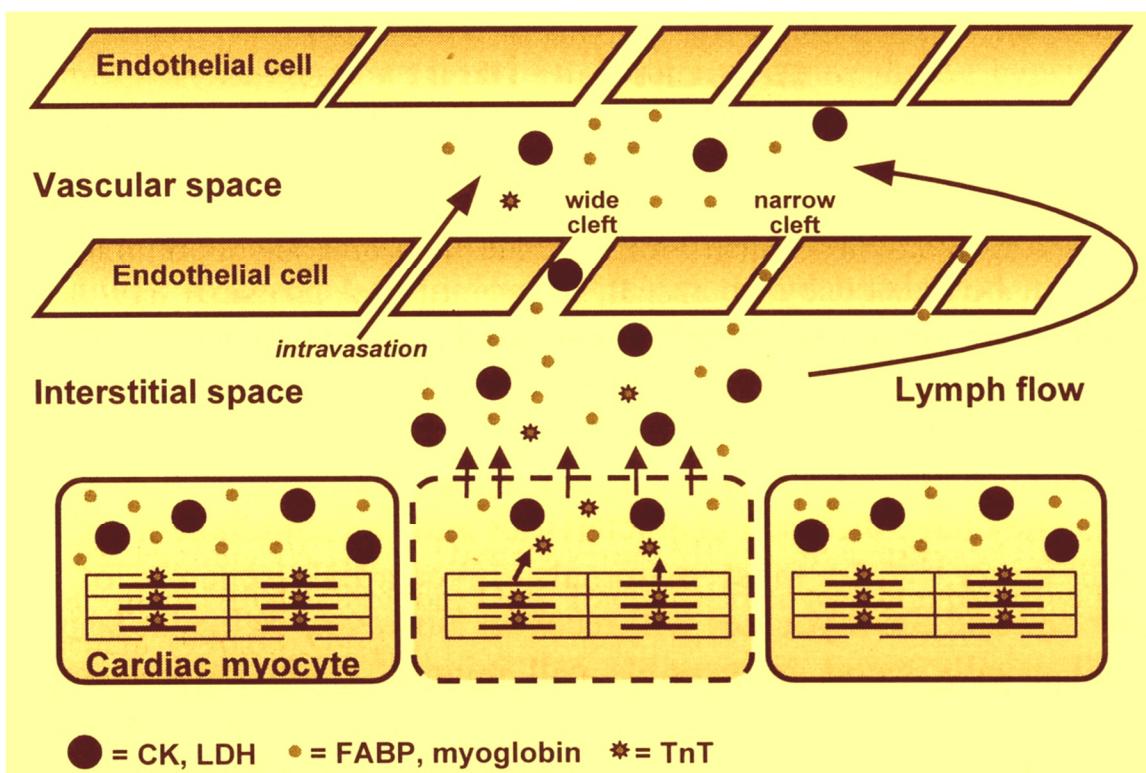
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Arguments supporting the benefits and advantages of human  
**heart-type fatty acid-binding protein (h-FABP)**  
as early marker for acute myocardial infarction (AMI)

When minutes count ...

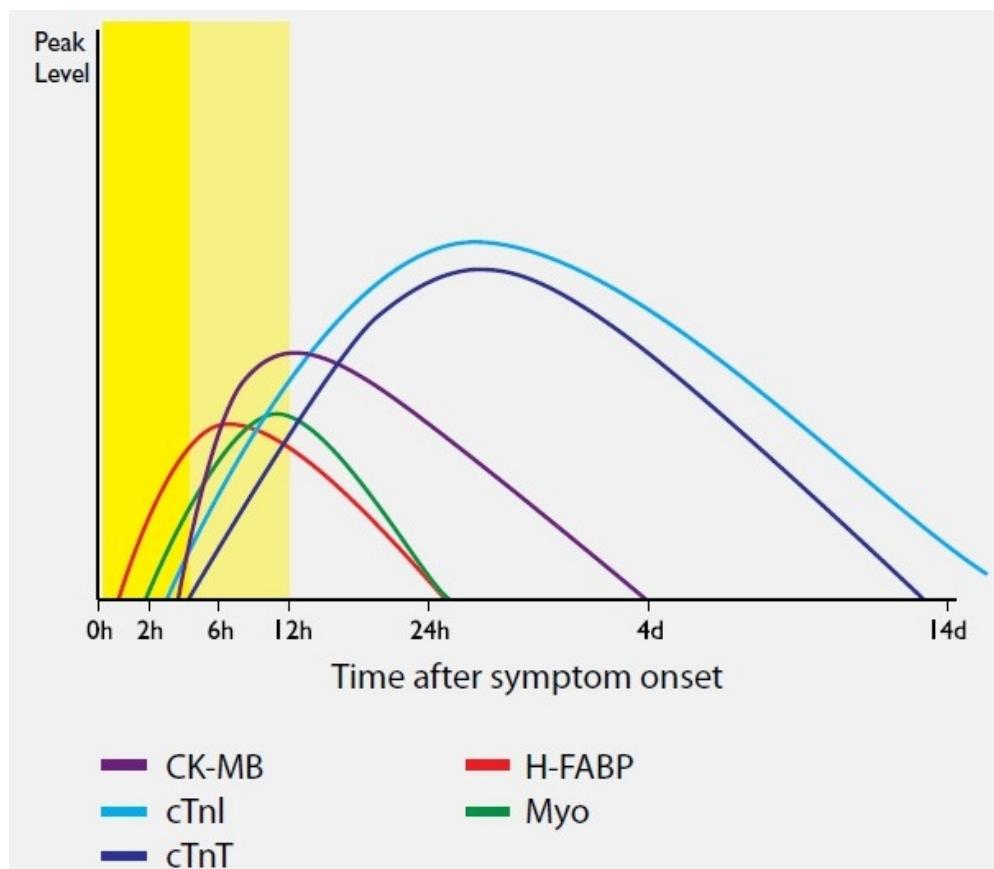
h-FABP is a small protein (15 kDa) abundantly present in myocardial cells. It is involved in the intracellular uptake and transport of long-chain fatty acids. Due to the small size **and** the cytoplasmic localisation it is rapidly released into the circulation after myocardial cell damage.

The possible transport routes of proteins released from damaged cardiac myocytes to the plasma compartment are shown below. Proteins can either cross the endothelial cell barrier directly (predominant route for **small proteins** such as **h-FABP** and Myoglobin) or they can be transported through lymph drainage (predominant route for larger proteins such as Creatine-Kinase (CK) and Lactate Dehydrogenase (LDH)). **Structurally bound proteins** (such as **Troponins**) **must be dissociated** first from the myofibrillar structures before they can be released into the interstitial space<sup>1</sup>.



<sup>1</sup> Van der Voort D: Development of an immunosensor for on-line continuous measurement of cardiac injury. Thesis (2003), Maastricht University, 16

Based on the release mechanism the following time course can be observed for the different cardiac markers after AMI<sup>2</sup>:



The diagnostic potential of h-FABP was first reported by Prof. Glatz (Maastricht University, The Netherlands) in 1988<sup>3</sup>. In the meantime many studies have confirmed that **h-FABP is a promising early marker of myocardial damage and improves diagnosis of AMI and risk stratification.**

The h-FABP advantages in a nutshell:

- Early release due to cytoplasmic location
- Therefore, detectable as early as 30 minutes after ischemic episode<sup>4</sup>
- Rapid increase from base levels to clinical cut-off value, even faster than Myoglobin<sup>5</sup>
- Furthermore, low normal plasma value
- Extremely stable protein

<sup>2</sup> Data source: <http://www.randox.com/brochures/PDF%20Brochure/LT237.pdf>

<sup>3</sup> Glatz JFC, van Bilsen M, Paulussen RJA, et al.: Biochem Biophys Acta (1988), 961, 148-52

<sup>4</sup> Kleine AH, Glatz JF, van Nieuwenhoven FA, van der Vasse GJ: Release of heart type fatty acid binding protein into plasma after acute myocardial infarction in man. Mol Cell Biochem (1992), 116, 155-162

<sup>5</sup> Pelsers MM, Hermens WT, Glatz JF: Fatty acid-binding proteins as plasma markers for tissue injury. Clin Chem Acta (2005), 352 (1-2), 15-35

Particularly in the first hours after onset of AMI symptoms h-FABP is superior compared to contemporary Troponin (I) assays<sup>6</sup> (NPV = negative predictive value; AUC area under the ROC curve):

Sensitivity	0-3 hrs	3-6 hrs	6-12 hrs	12-24 hrs
cTnI	50%	68%	81%	96%
H-FABP	64%	85%	90%	90%
Specificity	0-3 hrs	3-6 hrs	6-12 hrs	12-24 hrs
cTnI	93%	94%	94%	94%
H-FABP	84%	89%	94%	91%
NPV	0-3 hrs	3-6 hrs	6-12 hrs	12-24 hrs
cTnI	92%	95%	97%	99%
H-FABP	93%	97%	98%	99%
AUC	0-3 hrs	3-6 hrs	6-12 hrs	12-24 hrs
cTnI	0.76	0.85	0.90	0.98
H-FABP	0.84	0.89	0.94	0.97

In order to reduce the “Troponin-blind phase” at the beginning of a heart attack **high sensitive assays** were developed in the recent past. The clinical sensitivity of the mentioned tests is much higher than for the contemporary Troponin assays, especially in the early phase of an AMI. However, the **increased sensitivity** (95 %) comes along with a **reduced clinical specificity** (80 %) and a lower positive predictive value (PPV 50 % (NPV 95 %))<sup>7</sup>. Before reducing the test-specific cut-off (e.g. from 100 to 14 pg/ml for Troponin T) it was an established doctrine that Troponins (T and I) are absolutely specific markers for cardiac muscle damage and AMI. With the high sensitive assays the lower measuring range was expanded into regions which were not detectable a short while ago. This fact is caused by the problem that the **very low Troponin concentrations** measureable now (picogram range → down to 0.000 000 000 014 grams/ml), can **have other origin than AMI**. Slightly increased Troponin levels may also be due to: abnormally fast heart beat, high blood pressure in lung arteries (pulmonary hypertension), blockage of a lung artery (by a blood clot, fat, or tumour cells (pulmonary embolus)), congestive heart failure, coronary artery spasm, inflammation of the heart muscle usually due to a virus (myocarditis), strenuous exercise (for example, due to marathons or triathlons),

<sup>6</sup> McMahon CG, Lamont JV, Curtin E, McConnell RI, Crockard M, Kurth MJ, Crean P, Fitzgerald SP: Diagnostic accuracy of heart-type fatty acid-binding protein for the early diagnosis of acute myocardial infarction. Am J Emerg Med (2012), Feb 30(2), 267-74

<sup>7</sup> Reichlin *et al.*, N Eng J Med (2009), 361, 858-67

trauma that injures the heart such as a car accident, weakening of the heart muscle (cardiomyopathy). Increased Troponin levels may also result from certain medical procedures such as: cardiac angioplasty/stenting, heart defibrillation or electrical cardioversion (purposeful shocking of the heart by medical personnel), open heart surgery and radiofrequency ablation of the heart. This **loss of clinical specificity was** clearly **verified** at the congress of the American Association for Clinical Chemistry (AACC) in 2010. Ferreira C.E. *et al.* from the Hospital Albert Einstein, São Paulo, Brazil have presented results from a clinical study with the objective: to evaluate the routine Troponin I in a general hospital and correlate it with clinical situations (Poster C-35). 4.559 Troponin I tests were done and 1.540 tests (33.78 %) had values above the high sensitive cut-off point (34 pg/ml for Troponin I). The main differential diagnosis of patients with test results above the cut-off was composed as follows:

- ACS : 25%
- Cardiac surgery : 7.8%
- Cardiac catheterization : 2.4%
- Angioplasty : 5.2%
- Heart failure- NO AMI : 7.7%
- Chest pain : 7%
- Arrhythmia : 5.7%
- Respiratory failure : 5.7%
- Non cardiac surgery : 5%
- Sepsis : 4.3%
- Infectious processes : 3.4%
- Acute pulmonary edema : 2.7%
- Hypertension, pulmonary thromboembolism, kidney failure death : 0-2% each
- Cancer, transplantation, diabetes, and other disease situations : 13%

These data demonstrate the loss of clinical specificity impressively. Similar results were published from Koerbin G. *et al.*<sup>8</sup>. A **cardio-healthy** reference **population** was investigated using the new **high sensitive Troponin T** assays. **Approximately 42%** of the samples showed Troponin T **concentrations above** the manufacturer's quoted **limit of detection**. The authors conclude that with many apparently healthy people having detectable Troponin, clinical judgement will become more important in interpreting Troponin results.

For the high and ultra-high sensitive Troponin assays it can be summarized:

**increased sensitivity leads to decreased clinical specificity**

and this is the other side of the coin with respect to the challenge of cut-off optimization.

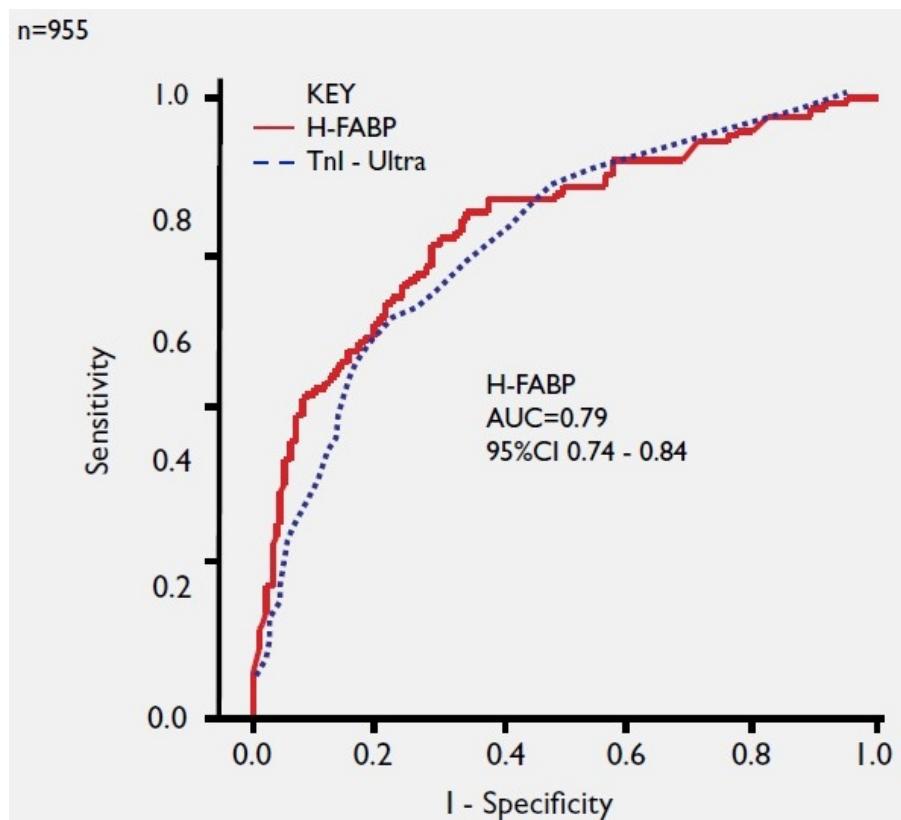
**However, there is no need to accept a loss of specificity in the first hours after onset of AMI symptoms. The solution to this problem has a name: h-FABP!**

The **benefits of h-FABP** are **evident**, even when used **in addition to a high sensitive Troponin** assay (Siemens Advia Ultra-TnI) that meets the ACC/ESC guidelines. Viswanathan *et al.*<sup>9</sup> have shown that the receiver-operator curves (ROC) for h-FABP and ultra-TnI in the prediction of death or AMI have a significantly higher area under the curve for h-FABP (0,79) than for ultra-TnI (0,77).

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<sup>8</sup> Koerbin G *et al.*, Annals of Clinical Chemistry (2010), 47, 524-28

<sup>9</sup> Viswanathan K, Kilcullen N, Morrell C, Thistlethwaite SJ, Sivananthan MU, Hassan TB, Barth JH, Hall AS: heart-type fatty-acid binding-protein (H-FABP) predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome .J Am Coll Cardiol (2010),55(23),2590-8



**Attention should also be paid to the fact that a combination of h-FABP and Troponin (I) can be used effectively as rule-out test to exclude AMI within 6 hours of pain onset.**

In a study with a total of 1128 patients (providing 2924 venous blood samples) McMahon *et al.*<sup>10</sup> have evaluated the diagnostic efficacy of multiple tests – heart-type fatty acid-binding protein (h-FABP), cardiac troponin I (cTnI), creatine kinase-MB, and myoglobin – for the early detection of acute myocardial infarction among patients who present to the emergency department with chest pain. The results can be summarized as follows:

- **h-FABP** had the **greatest sensitivity** at 0 to 3 hours (64.3%) and 3 to 6 hours (85.3%) after chest pain onset
- the **combination** of **cTnI** measurement with **h-FABP increased sensitivity** to 71.4% at 3 to 6 hours and 88.2% at 3 to 6 hours

<sup>10</sup> McMahon CG, Lamont JV, Curtin E, McConnell RI, Crockard M, Kurth MJ, Crean P, Fitzgerald SP: Diagnostic accuracy of heart-type fatty acid-binding protein for the early diagnosis of acute myocardial Infarction, AmJ Emerg Med ( 2012 ), Feb 30 (2), 267-74

- receiver operating characteristic curves demonstrated that **h-FABP** had the **greatest diagnostic ability** with area under the curve at 0 to 3 hours of 0.841 and 3 to 6 hours of 0.894
- the **specificity** was also **high** for the **combination** of h-FABP with cTnI at these time points
- **h-FABP** had the **highest negative predictive values** of all the individual markers: 0 to 3 hours (93%) and 3 to 6 hours (97%)
- the **combined measurement** of cTnI with h-FABP **increased** the **negative predictive values** to 94% at 0 to 3 hours, 98% at 3 to 6 hours, and 99% at 6 to 12 hours.

Therefore, it can be concluded that **testing both** h-FABP and cTnI provides a reliable diagnostic tool for the early diagnosis of myocardial infarction/acute coronary syndrome and also a **valuable rule-out test** for patients presenting at 3 to 6 hours after chest pain onset.

Time post pain	NPV in %			
	0-3h	3-6h	6-12h	12-24h
Individual markers				
H-FABP	93	97	98	99
cTnI	92	95	97	99
2 marker combinations				
H-FABP + cTnI	94	98	99	100

Time saves heart muscle ...

Against this background it should be mentioned that the high and ultra-high sensitive Troponin assays are dependent on (modular) analysers, which are not suitable for point of care and bedside diagnostic.

In contrast the lateral flow device **QuickSens®h-FABP** fulfilled the requirements of the primary care market with respect to:

- available equipment,
- **time-to-result** and
- simplicity of workflow.



Review

# Heart-Type Fatty Acid-Binding Protein (H-FABP) and Its Role as a Biomarker in Heart Failure: What Do We Know So Far?

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**Abstract:** Background: Heart failure (HF) remains one of the leading causes of death to date despite extensive research funding. Various studies are conducted every year in an attempt to improve diagnostic accuracy and therapy monitoring. The small cytoplasmic heart-type fatty acid-binding protein (H-FABP) has been studied in a variety of disease entities. Here, we provide a review of the available literature on H-FABP and its possible applications in HF. Methods: Literature research using PubMed Central was conducted. To select possible studies for inclusion, the authors screened all available studies by title and, if suitable, by abstract. Relevant manuscripts were read in full text. Results: In total, 23 studies regarding H-FABP in HF were included in this review. Conclusion: While, algorithms already exist in the area of risk stratification for acute pulmonary embolism, there is still no consensus for the routine use of H-FABP in daily clinical practice in HF. At present, the strongest evidence exists for risk evaluation of adverse cardiac events. Other future applications of H-FABP may include early detection of ischemia, worsening of renal failure, and long-term treatment planning.

**Keywords:** H-FABP; heart-type fatty acid-binding protein; FABP3; fatty acid-binding protein 3; heart failure; HF; cardiac biomarkers

## 1. Introduction

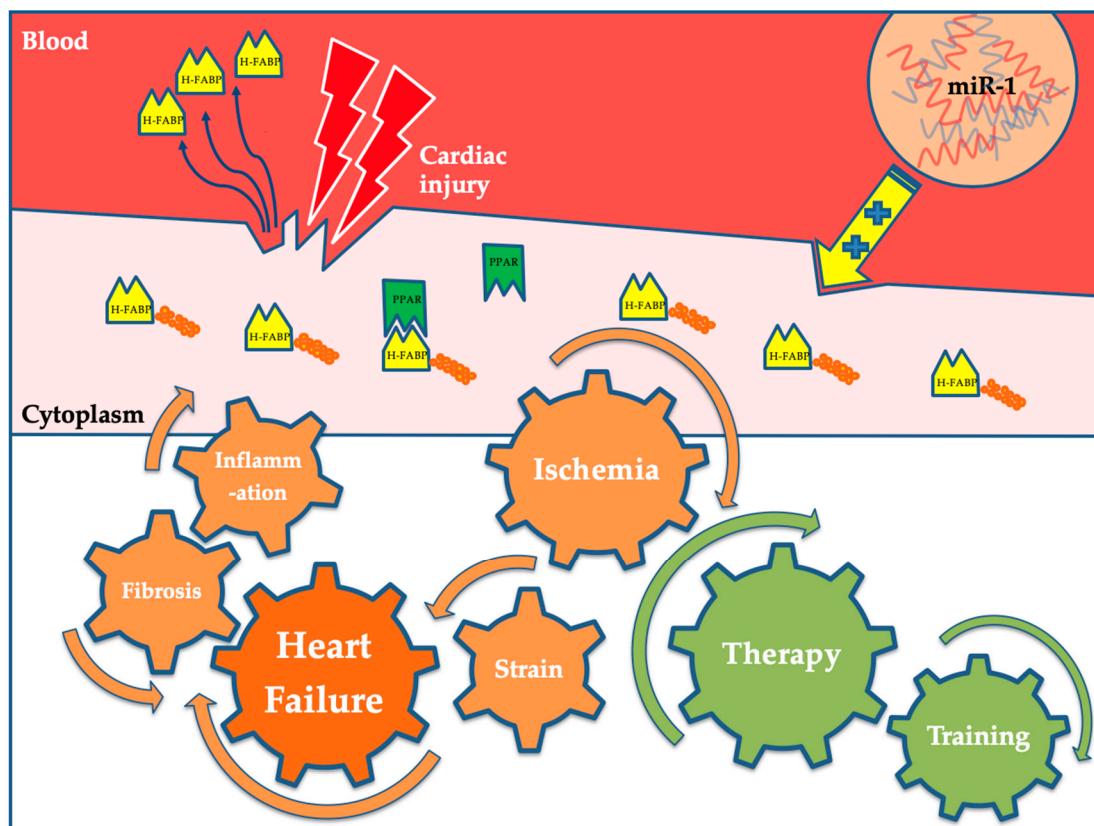
According to the Global Burden of Disease study, cardiovascular (CV) diseases represent the leading cause of death among non-communicable diseases, accounting for approximately 17.9 million deaths worldwide in 2015 [1]. As described in the meta-analysis by Van Riet et al., the prevalence of all-type heart failure (HF) in the older cohort of patients (>60 years) is 11.8% [2]. Additionally, health care costs, related to HF, represent a serious economic burden to healthcare systems. Heidenreich and colleagues estimated that the total medical costs of HF in the US will increase from \$31 billion in 2012 to at least \$70 billion in 2030 [3]. Thus, it is not only important to find new therapeutic approaches, but also to diagnose affected individuals early and monitor therapies properly. Biomarkers for HF are subject of current research and may have the potential to, not only reduce costs, but also extend symptom-free intervals through effective therapy control.

Described for the first time in 1972, a group of cytoplasmic proteins called fatty acid-binding proteins (FABPs) has been under investigation in the scientific community [4]. To date, several subtypes of FABPs, occurring in various organ systems in different concentrations, have been discovered. These low-molecular-weight proteins (about 15 kD [5]) have been widely discussed, especially given the association of H-FABP as an independent risk factor for all-cause mortality and cardiovascular (CV) death [6]. According to the HUGO Gene Nomenclature Committee, the FABP family consists of 16 members, each encoded by a distinct gene. The probably best-known members include L- (liver), I- (intestinal), H- (muscle/heart), A- (adipocyte), E- (epidermal), Il- (ileal), B- (brain), M- (myelin), and T-FABP (testis) [7]. FABPs are involved in cellular fatty acid metabolism as they reversibly bind and transport long-chain polyunsaturated fatty acids (PUFA) from cell membranes to the mitochondria. Additionally, they contribute to cellular growth and proliferation processes, and can activate peroxisome proliferator activated receptors (PPARs). Therefore, they play a functional role in lipid metabolism and energy homeostasis [8–10].

The heart-type FABP (H-FABP), also known as mammary-derived growth inhibitor, is probably the best-known member of the FABP family. H-FABP is encoded by the FABP3 gene located on the 1p33-p32 region of chromosome 1 [11], whereas, RXRa, KLF15, CREB, and Sp1 were identified as transcriptional factor binding sites for different PPARs in animal studies [12]. It is expressed in tissues with high demand of fatty-acids, such as heart, skeletal-muscle, brain, kidney, adrenal gland, and mammary gland tissues, as well as in blastocysts [8]. FABP3 was also found to be expressed in  $\gamma$ -aminobutyric acid (GABA)-ergic inhibitory interneurons of the male anterior cingulate cortex in mice, suggesting that it has an important role also in cerebral PUFA-homeostasis [13]. H-FABP itself is abundant in the cytoplasm of striated muscle cells and is rapidly released in response to cardiac injury [14]. H-FABP is expressed more abundantly in the heart's ventricles (0.46 mg/g wet weight) and atria (0.25 mg/g wet weight) than in skeletal muscles (e.g., the diaphragm contains 25% of the heart's H-FABP concentration) or in other organs (less than 10% of the H-FABP content of the heart) [15]. In healthy individuals, serum levels of H-FABP are in the single digit ng/ml range [16–18]. Expression of H-FABP is regulated by the microRNA miR-1, which might play a role in the progression of HF itself [19]. Upon myocardial injury, H-FABP is rapidly released from myocytes into the systemic circulation, due to its small size and free cytoplasmic localization. Also, transient increases in sarcolemmal membrane permeability are suspected to permit H-FABP leakage into the systemic circulation [20,21]. This so-called "wounding" of myocytes was observed, even after short-term ventricular stress, and it may play an important role in diverse auto- and paracrine mechanisms in the pathogenesis of HF [20]. The elimination of H-FABP takes place via the kidney, explaining a shorter diagnostic window in patients with normal renal function [22]. Kleine et al., for example, reported that H-FABP plasma levels returned to baseline within 20 hours after the onset of symptoms in patients with acute myocardial infarction [23].

Apart from its crucial role in cardiac lipid transport [24,25], several in vitro and in vivo studies investigated further functions of H-FABP. The potential role of H-FABP in cardiomyocyte differentiation was suggested by Tang et al., who observed a correlation between H-FABP expression and decreased cell proliferation in mouse cardiomyocytes [26]. A similar finding was obtained by Wang et al., using human bone marrow derived mesenchymal stem cells, by which overexpression of H-FABP inhibited proliferation [27]. Additionally, it was shown by Zhu et al., using a P19 embryonic myocardial cell line overexpressing H-FABP, that it might inhibit cell proliferation and promote apoptosis during myocardial cell development [28]. However, in a later study, H-FABP silencing instead of overexpression led to reduced proliferation and increased apoptosis in the same cell line [29]. In zebrafish, the knock-down of H-FABP resulted in impaired heart development and augmented apoptosis [30,31]. In neonatal rats, H-FABP downregulation repressed cell apoptosis and improved structural remodeling in ventricular myocytes under hypoxia. On the other hand, H-FABP upregulation enhanced phosphorylation of the MAPK signalling pathway and decreased phosphorylated protein kinase B (Akt) levels, increasing apoptosis and remodeling [32]. An anti-apoptotic role of H-FABP was also found in hypoxia/reoxygenation induced H9c2 cardiomyocytes [33]. Consistent with this,

H-FABP enhanced survival in human bone marrow derived mesenchymal stem cells in hypoxia [27]. Overexpression of H-FABP promoted growth and migration in human aortic smooth muscle cells [34]. In summary, the precise mechanism by which this protein influences cardiomyocyte proliferation and apoptosis remains elusive and further research is needed to explain its mode of action. Figure 1 provides a graphic overview of H-FABP under physiological and pathophysiological conditions.



**Figure 1.** Under physiological conditions, H-FABP serves as a transport protein in cellular metabolism and can reversibly bind fatty acids. Furthermore, it can activate PPARs and therefore plays a role in lipid metabolism and energy homeostasis. The expression of H-FABP is regulated by the microRNA miR-1. In response to cardiac injury, H-FABP is rapidly released into the blood-stream where it can be quantified. Physical training as well as pharmacological interventions like anti-tachycardic therapy were shown to decrease plasma levels of H-FABP. Abbreviations: miR-1: microRNA 1; PPAR: peroxisome proliferator activated receptor (PPAR). H-FABP: heart-type fatty acid-binding protein.

Regarding laboratory testing, different types of assays are frequently used in research and clinical settings for the detection and quantification of H-FABP in serum, plasma, or whole blood. These assays comprise enzyme-linked immunosorbent assays (ELISA) [6,15,35–37], immunoturbidimetric assays [38,39], multiplex assays [40,41], and immunochromatographic assays [42,43]. Test times depend on the type of assay, and vary between 5 and 120 min (as reviewed in [44]). The varying characteristics of these tests allow flexibility when choosing the appropriate test for the desired readout under varying budget and time restrictions.

A number of authors have discussed the role of H-FABP in clinical routine since its discovery. The following literature review will consider H-FABP and its potential use as a biomarker in HF.

## 2. Methods

A structured database search regarding H-FABP and its role in HF was conducted using “PubMed Central”. Three researchers (R.R., M.G. and R.D.) screened the studies independently. To select possible

studies for inclusion in the definite analysis, the authors screened all available studies by title and, if suitable, by abstract. Manuscripts that appeared relevant were read in full text. References of studies included were reviewed for further reading. This review on H-FABP in HF was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [45]. The corresponding flow-chart is given in Appendix A Figure A1.

### 3. H-FABP as a Biomarker in Heart Failure

According to the European Society of Cardiology (ESC) guidelines, HF is a syndrome characterised by typical symptoms and clinical signs, with a “structural and/or functional cardiac abnormality” as an underlying cause, “resulting in reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress” [46]. Due to their strong negative-predictive value, the use of natriuretic peptides is well-established in standard HF algorithms [46–48]. Nevertheless, like many other biomarkers, including cardiac troponins, elevated levels of B-type natriuretic peptide (BNP) may also indicate alternative conditions and BNP release may lag in conditions with very acute onset, such as flash pulmonary edema or right-sided acute HF (AHF) [46,49]. As mentioned in the actual ESC-guidelines, their use for ruling out HF, but not for setting up the diagnosis, can be recommended [46]. These guidelines also state that, despite extensive research, no recommendation can currently be made for the use of novel cardiac biomarkers in everyday clinical practice [46]. The same holds true for the American AHA guidelines on HF [47] and even a specific sub-study of the large scale PROTECT trial failed to identify the perfect single biomarker among 48 different markers for the prognostic assessment of patients with AHF [50].

Most biomarkers are not indicative of cardio-specific events but of general pathologic processes like inflammation, ischemia, fibrosis, or general cell death. As HF is an aetiologically diversified, systemic-progressive disease, a simultaneous assessment of different pathways seems reasonable, though, a prognostic assessment based on a single factor is challenging. Possible hallmarks in the pathophysiology of HF are mechanical stress, ischemia, chronic (subclinical) inflammation, fibrosis, and angiogenesis [36]. With respect to ischemic heart disease, the potential suitability of H-FABP as an early indicator of myocardial injury has been mentioned for years in numerous publications. In contrast to cardiac troponins, which are bound to the myocyte’s structural apparatus, H-FABP is present as soluble protein in the cytoplasm. Therefore, the release into systemic circulation may possibly be detected more rapidly and even after minor myocardial damage [21]. Liebetrau et al., for example, report significantly increased serum levels of H-FABP already 15 minutes after iatrogenic myocardial infarction, caused by transcoronary ablation of septal hypertrophy (TASH). in patients with hypertrophic obstructive cardiomyopathy [14]. Some authors state additional benefits of combining H-FABP with high-sensitive troponins [37,38], whereas, others do not conclude any incremental benefit of H-FABP on top of cardiac troponins for diagnosing acute myocardial infarction [42,51,52]. Regarding pulmonary embolism (PE), several publications describe the use of H-FABP for risk stratification due to its role as an early indicator of right-ventricular strain [53–55]. A strong correlation with the risk of major adverse events and mortality was demonstrated, and even the 2019 ESC Guidelines on the diagnosis and management of acute PE mention the use of H-FABP for risk stratification, despite the fact that prospective trials are still missing [56].

As mentioned before, H-FABP plays an important role in cellular signalling, lipid-transport, and myocytal homeostasis [57]. Additionally, due to the amphipathic nature of fatty acids, their accumulation and membranal storage can have noxious effects on cellular structural and functional properties [57]. Therefore, mechanical stress, as well as cellular damage, including from ischemic or inflammatory processes, may be further perpetuated by a disturbed myocytal homeostasis, reduced intracellular H-FABP content [11], and may support the (chronically) progressive character of HF. Despite its rapid, and in the case of CHF, sustained release into general circulation, H-FABP not only acted as an indicator of cellular damage, but also a marker of myocytal dyshomeostasis, and thus, functional impairment of the myocardium.

Various authors have investigated the role of H-FABP in patients suffering from HF with different methods over the last few years. Many studies postulate the independent relationship between H-FABP and outcome, as well as the risk of adverse CV events [40,58–61]. In a recent study by Ho et al., for example, high levels of H-FABP were an independent risk factor for CV death and acute HF-related hospitalization in 1071 patients with chronic coronary disease [40]. In an interesting study from 2005 with 186 patients, Niizeki et al. demonstrated superiority of the combined analysis of BNP and H-FABP for risk stratification in patients with CHF. The authors described the added benefit of H-FABP in showing persistent myocardial damage, compared to BNP, as a sole myocardial strain parameter. Interestingly, the authors only found a weak correlation between the two individual laboratory parameters, which may indicate different pathophysiological origins [58]. In a second study from 2008, involving 113 patients with CHF, the authors again associated persistently high levels of H-FABP with adverse events in patient follow-up. They suggested serial measurement of H-FABP concentrations for therapy monitoring, as they observed regredient serum levels under HF therapy in a subgroup of patients [59]. A significant decrease in H-FABP levels was also observed in a study by Jirak et al. where they investigated several biomarkers in fifty patients with CHF under therapy with the If channel inhibitor, ivabradine [62]. This was also observed in children with CHF after treatment with carvedilol [63].

Regarding AHF, Hoffmann et al. found improved specificity and positive predictive value for the diagnosis of AHF in their work including 401 patients with acute dyspnea or peripheral edema when using H-FABP in addition to BNP. H-FABP levels also correlated with adverse outcomes and AHF related rehospitalization [60]. These findings are in line with the work of Ishino et al. In their study on 134 patients with acute decompensated HF (ADHF), the authors were able to correlate high H-FABP levels with significantly higher rates of adverse cardiac events and in-hospital mortality [61]. Kazimierczyk et al. observed significantly higher rates of death and rehospitalization in patients with ADHF and both higher H-FABP concentrations at admission and discharge. Echocardiographic remodeling parameters correlated well with high initial H-FABP-levels [64]. Shirakabe et al. were able to correlate serum H-FABP levels not only with all-cause mortality in patients with ADHF, but also worsening of renal failure. The latter finding achieved a sensitivity and specificity of 94.7%, and 72.7%, respectively (AUC = 0.904) in non-chronic kidney disease patients [65].

Concerning patients with HF with reduced ejection fraction (HFrEF), Lichtenauer et al. enrolled 65 patients with dilative cardiomyopathy (DCM) and 59 patients with ischemic cardiomyopathy (ICM) in their study on novel cardiac biomarkers in CHF. H-FABP levels were significantly elevated in both patient populations, compared to controls without signs of HF or coronary artery disease. Furthermore, H-FABP levels not only correlated proportionally with NYHA functional class, but also inversely with ejection fraction [36]. Regarding HF with preserved ejection fraction (HFpEF; left ventricular ejection fraction  $\geq 50\%$ ), Kutsuzawa et al. observed an independent correlation of higher H-FABP-levels and the occurrence of adverse CV events in their study on 151 HFpEF-patients. Interestingly, serum levels of H-FABP did not differ between patients with HFpEF and HFrEF (left ventricular ejection fraction  $< 50\%$ ) between each NYHA functional class [66]. Dinh et al. found markedly higher levels of Troponin T and H-FABP, even in patients with asymptomatic left ventricular diastolic dysfunction and patients with HF and normal ejection fraction, supposing ongoing myocyte damage in these patient collectives [67]. However, Jirak et al. observed significantly higher H-FABP serum levels in patients with DCM and ICM, than in patients with HFpEF. Nevertheless, significantly higher H-FABP concentrations were shown in HFpEF patients compared to the control group [68].

Considering patients with valvular heart disease, Iida et al. showed an independent association of H-FABP with clinical outcomes in hypertensive patients with aortic valve disease. Echocardiographically determined left ventricular dimensions were signs of cardiac remodelling and correlated significantly with measured levels of H-FABP, whereas Troponin T remained below cut-off levels in all patients [21]. Mirna et al. actually reported a significant reduction in H-FABP plasma concentration in 79 patients with severe aortic valve stenosis after conducting transcatheter aortic valve

implantation (TAVI), indicating reduced ventricular wall stress and potential reversibility of cardiac remodeling due to valvular replacement [69].

Regarding arrhythmia as a co- and sometimes main-perpetrator in HF, Otaki et al. observed in their study with 402 patients higher levels of H-FABP in patients with CHF and atrial fibrillation (AF) than in patients with CHF and sinus rhythm (SR) [70]. Rader et al. showed that in 63 studied patients undergoing cardiac surgery that post- but not preoperative H-FABP levels correlated with onset of perioperative AF (POAF) [71]. Interestingly, Shingu et al. observed lower H-FABP gene expression in patients' atria with POAF after cardiac surgery, illustrating the complexity of cellular processes in the development of HF [72].

Mirna et al. made another interesting discovery when investigating H-FABP levels in patients with pulmonary hypertension (PH). They observed that H-FABP levels were primarily elevated in group two and three PH, namely PH related to left heart disease, pulmonary disease, and chronic hypoxia. H-FABP may, therefore, be useful as a possible indicator for post-capillary PH [73].

Application of H-FABP measurement in HF monitoring may also be found in paediatric cardiology. Zoair et al. reported a correlation of serum H-FABP levels with clinical and echocardiographic signs before, and after, HF therapy in 30 children with congestive HF compared to 20 healthy individuals. An unfavourable outcome was again associated with increased serum levels. However, the study was limited as H-FABP was investigated as a single laboratory parameter, and its superiority over biomarkers, such as BNP, was not determined [74]. Sun et al. also reported that there is a correlation between H-FABP levels with disease severity in children with CHF, but again other laboratory markers were not compared [75]. In their study on 238 children and adolescents with congenital heart disease, Hayabuchi et al. found that H-FABP did not correlate with BNP, but was affected by age, NYHA class, arterial oxygen saturation, CK-MB and creatinine, supporting a different pathophysiological pathway of the two biomarkers [76]. Table 1 gives an overview of selected studies on H-FABP and HF.

**Table 1.** Overview of different positive clinical studies assessing the diagnostic value of H-FABP (heart-type fatty acid-binding protein) in patients with heart failure (HF) (sorted by main topic and year of publication).

Main Findings	Study	Patient Number	Reference
High H-FABP (>4.3 ng/mL) and elevated BNP (>200 pg/mL) showed highest rates for cardiac death and cardiac events and were also independent predictors of cardiac events (H-FABP HR 5.416, $p = 0.0002$ ; BNP HR 2.411, $p = 0.0463$ )	Prospective study for 534+/-350 days on CHF patients	186	Niizeki T. et al., 2005 [58]
Persistently high H-FABP levels at hospital discharge (>4.3 ng/mL) correlated with increased rates for CV events (HR 5.68)	Prospective study for 624+/-299 days on patients with CHF	113	Niizeki T. et al., 2008 [59]
Two-fold higher rate of primary CV events between high H-FABP (>4.143 ng/mL) vs. low H-FABP group (32% vs. 16% respectively)	Prospective multicenter study for 24 months on patients with stable coronary heart disease (SCHD)	1071	Ho S. et al., 2018 [40]
H-FABP levels of >5.7 ng/mL were correlated with significantly higher in-hospital mortality (6.7% vs. 0%, $p < 0.05$ ) and cardiac events	Study for 615 days on patients with ADHF	134	Ishino M. et al., 2010 [61]
Highest H-FABP level patient quartile showed increased all-cause mortality (HR: 2.1–2.5, $p = 0.04$ ) and AHF related rehospitalization rate (HR 2.8–8.3, $p = 0.001$ ); combining H-FABP & NT-proBNP improves diagnostic specificity and PPV to rule out AHF	Prospective study for up to five years on patients with acute dyspnea or peripheral edema with or without AHF	401	Hoffmann U. et al., 2015 [60]
Significant positive correlation between H-FABP with echocardiographic parameters, death and rehospitalization	Study on patients with ADHF	77	Kazimierczyk E. et al., 2018 [64]
Serum H-FABP levels were significantly higher in patients with true worsening renal failure	Retrospective study on patients with AHF	281	Shirakabe A. et al., 2019 [65]
H-FABP levels are significantly higher in patients with DCM and ICM; ejection fraction correlates inversely with H-FABP concentrations	Study on the diagnostic value of novel cardiac biomarkers in patients with HFrEF	65 patients with DCM, 59 patients with ICM, 76 controls	Lichtenauer M. et al., 2017 [36]

**Table 1.** Cont.

Main Findings	Study	Patient Number	Reference
Significantly higher levels of Troponin T and H-FABP in patients with asymptomatic LVDD and patients with HFnEF	Study on patients with HFnEF	49 patients with HFnEF, 51 patients with asymptomatic LVDD, 30 controls	Dinh W. et al., 2011 [67]
Higher H-FABP-levels correlated with adverse CV events; H-FABP levels did not differ between patients with HFpEF and HFrEF between each NYHA functional class	Prospective study on patients with HFpEF with a median follow-up of 694 days	151 patients with HFpEF, 162 patients with HFrEF as controls	Kutsuzawa D. et al., 2012 [66]
A greater rise in post-operative H-FABP levels is associated with AF after cardiac surgery	Prospective study on patients undergoing cardiac surgery	63	Rader F. et al., 2013 [71]
Optimal cut-off values for H-FABP as myocardial damage marker were higher in CHF patients with AF than in patients with SR (5.4 vs. 4.6 ng/mL)	Prospective study on patients with CHF and AF or CHF and SR with a median follow-up of 643/688 days	402	Otaki Y. et al., 2014 [70]
H-FABP levels correlate independently with age, NYHA-class, CK-MB, creatinine and arterial oxygen saturation	Study in children and adolescents with congenital heart disease	238	Hayabuchi Y. et al., 2011 [76]
Significant negative correlation between H-FABP levels and heart function (LVEF, CI, LVSF)	Study in pediatric patients with chronic HF	36 patients and 30 healthy controls	Sun Y.P. et al., 2013 [75]
Significant positive correlation between increased H-FABP levels and severity of HF and adverse outcome	Prospective cohort study for 3 months on pediatric patients with HF	30 patients and 20 healthy controls	Zoair A. et al., 2015 [74]

Abbreviations: ADHF: acute decompensated heart failure; AF: atrial fibrillation; AHF: acute heart failure; BNP: brain natriuretic peptide; CHF: chronic heart failure; CK-MB: muscle-brain type creatine kinase; CI: cardiac index; CV: cardiovascular; DCM: dilative cardiomyopathy; HF: heart failure; HFnEF: heart failure with normal ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; ICM: ischemic cardiomyopathy; LVDD: left ventricular diastolic dysfunction; LVEF: left ventricular ejection fraction; LVSF: left ventricular shortening fraction; NYHA: New York Heart Association; PPV: positive predictive value; SR: sinus rhythm.

#### 4. Discussion and Conclusion(s)

In CV research, H-FABP represents a much-studied protein that is well-known for its role in lipid transport and influence on myocyte metabolism. Different assays and methods exist for measurement, allowing flexibility for the researcher and clinician. However, little is known about its precise function in cardiac development and remodelling. In vitro and animal studies suggest both, promoting and inhibitory roles in myocyte proliferation and apoptosis, but a mechanistic explanation is missing. If, and how, H-FABP that is released from damaged myocytes impacts the progression of HF and other CV diseases, in detail, remains unknown to date. Although, dyshomeostasis of cellular metabolism due to reduced intracellular H-FABP content, and hence, impaired fatty acid supply seems one reasonable consideration.

Individual investigators come to different conclusions about H-FABPs possible application in clinical routine. With BNP, a biomarker with high negative predictive value in differential diagnosis of HF and its long-term therapy surveillance already exists. The use of H-FABP in clinical settings has only been experimental in the past and large-scale studies are still lacking. Nevertheless, the different pathophysiological origins of H-FABP and BNP give hope for a more differentiated diagnostic approach in the future.

To date one possible application of H-FABP seems to be the detection of early and/or subclinical cardiac ischemia and inflammation. H-FABP could be used as a screening tool, for example, in routine health check-ups, since laboratory tests are inexpensive, and samples can be obtained in remote locations and analyzed in central laboratories. Takahashi et al. demonstrated a strong positive correlation between increased pulse pressure with BNP and H-FABP as signs of increased silent myocardial damage in 3504 participants at their annual health check [77]. On the other hand, the rapid detection of ischemia may pave the way for identifying patients with acute ischemia as an underlying cause of AHF at an early phase. As serum H-FABP levels were shown to correlate well with infarct size in patients with ST-elevation myocardial infarction [78], the measurement of H-FABP may enable the timely admission of revascularization procedures, and therefore, may even prevent the development of HF in the long run. As H-FABP and cardiac troponins show different release kinetics [14], a H-FABP-troponin ratio

may be useful for distinguishing acute ischemia from chronic myocardial damage in patients with decompensated HF.

Furthermore, interactions of the various organ systems in decompensated HF are highlighted by several authors and international guidelines [46,65,79]. As the coexistence of HF and chronic kidney disease is frequently observed, the terms “cardiorenal syndromes” as well as “renocardiac syndromes” have gained attention in the last few years. A peculiarity of H-FABP compared to markers, such as BNP and troponins, could lie in detecting true worsening of renal function [65]. The exact mechanism that causes this correlation has not yet been clarified. High levels of H-FABP in patients with ADHF may be due to severely decompensated HF itself, but also due to damage of the distal tubules or due to accumulation in glomerular podocytes. Nevertheless, as Shirakabe et al. note, this correlation has not previously been shown for BNP or troponins, which may give H-FABP a unique position as a biomarker in HF diagnostics [65].

Another application of H-FABP as a biomarker might be in highly specialized areas. Dalos et al. observed an exponential increase of H-FABP levels, with decreasing left ventricular ejection fraction in patients with coronary artery disease, reflecting chronic myocardial ischemia [80]. As a strong and independent correlation of H-FABP with individual prognosis was shown in several studies, it may, therefore, be used in mid- to long-term treatment planning. This may be especially helpful when dealing with invasive and expensive approaches, like implantable cardiac resynchronization devices, valve replacement, or mechanical circulatory devices. For example, Cabiati et al. demonstrate an association between high H-FABP levels and poor prognosis in patients after LVAD implantation [81].

The clinical picture of HF comprises a group of heterogenous disease entities as an underlying cause. Novel biomarkers extend our understanding both of CV physiology and pathophysiologic processes, leading to cardiac remodelling and the development of HF. By defining an appropriate patient population in the right clinical context, the additional diagnostic value of H-FABP as a biomarker in HF may well be obtained in the future. Furthermore, an optimal point in time for sample recovery, as well as different thresholds for diagnostic, prognostic, and therapeutic consequences need to be determined.

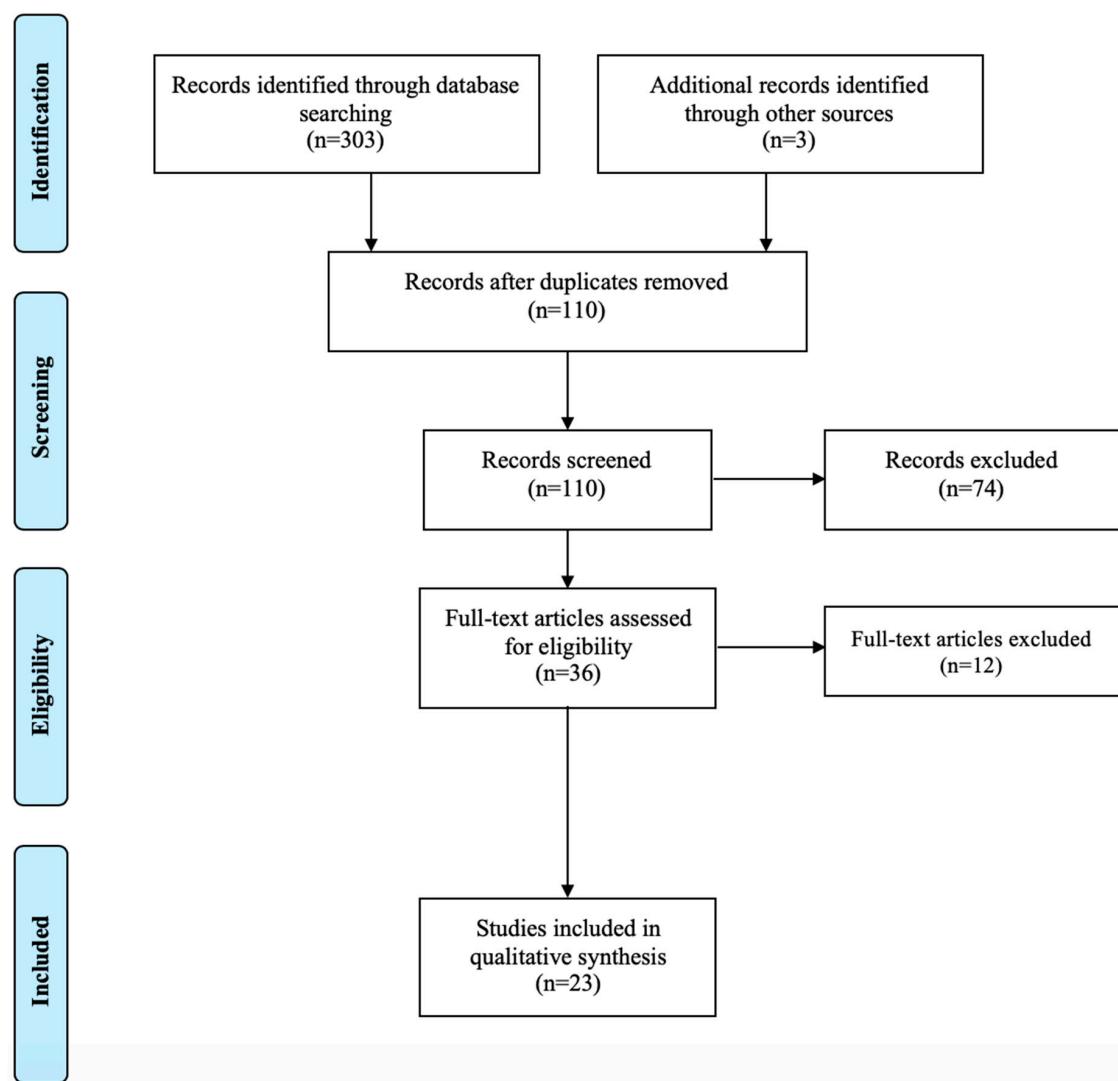
We currently assume that H-FABP is, not only a rapid indicator of myocardial ischemia, but that its loss from the cardiomyocytes' cytoplasm may cause an intracellular metabolic dyshomeostasis, and is therefore, conducive to the progressive nature of heart failure. H-FABP's present and future in HF diagnostics may also not lie in its use as a single laboratory value, but in a combination of clinical assessment, imaging, and a multi-biomarker approach.

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## Appendix A Flow Diagram



**Figure A1.** Flow diagram of the database search, screening and inclusion of the studies (modified after the PRISMA guidelines [45]).

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## Heart-type fatty acid-binding protein: an overlooked cardiac biomarker

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REVIEW ARTICLE



## Heart-type fatty acid-binding protein: an overlooked cardiac biomarker

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### ABSTRACT

Cardiac troponins (cTn) are currently the standard of care for the diagnosis of acute coronary syndromes (ACS) in patients presenting to the emergency department (ED) with chest pain (CP). However, their plasma kinetics necessitate a prolonged ED stay or overnight hospital admission, especially in those presenting early after CP onset. Moreover, ruling out ACS in low-risk patients requires prolonged ED observation or overnight hospital admission to allow serial measurements of c-Tn, adding cost. Heart-type fatty acid-binding protein (H-FABP) is a novel marker of myocardial injury with putative advantages over cTn. Being present in abundance in the myocellular cytoplasm, it is released rapidly (<1 h) after the onset of myocardial injury and could potentially play an important role in both earlier diagnosis of high-risk patients presenting early after CP onset, as well as in risk-stratifying low-risk patients rapidly. Like cTn, H-FABP also has a potential role as a prognostic marker in other conditions where the myocardial injury occurs, such as acute congestive heart failure (CHF) and acute pulmonary embolism (PE). This review provides an overview of the evidence examining the role of H-FABP in early diagnosis and risk stratification of patients with CP and in non-ACS conditions associated with myocardial injury.

### KEY MESSAGES

- Heart-type fatty acid-binding protein is a biomarker that is elevated early in myocardial injury
- The routine use in the emergency department complements the use of troponins in ruling out acute coronary syndromes in patients presenting early with chest pain
- It also is useful in risk stratifying patients with other conditions such as heart failure and acute pulmonary embolism.

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## Introduction

Chest pain (CP) is a common presenting complaint in emergency departments (ED), accounting for >5% of all visits, >7.5 million ED encounters/year in the US alone [1]. The most pressing concern in patients with CP is identifying acute coronary syndrome (ACS), i.e. patients with acute myocardial infarction (AMI) or unstable angina (UA), for a rapid institution of guideline-based therapy. Significant improvements in this regard over the last two decades have led to rates of missed AMI of less than 1–2% [2–4]. Conversely, among all-comers with CP, over half have “non-specific” CP, with 30% being admitted to the hospital and barely 5% eventually diagnosed with ACS, costing billions of dollars in unnecessary diagnostic testing and hospital stays [5].

Risk assessment of CP centers on history, electrocardiogram (EKG), and biomarkers. Aspartate transaminase (AST) was the first biomarker used in defining AMI in 1959 [6]. Since then several legacy biomarkers, including lactate dehydrogenase (LDH), myoglobin, creatine-kinase (CK), its cardiac-specific iso-enzyme CK-MB, were used, but they have been superseded by cardiac troponins (cTn) [7]. Though proven to be the most sensitive and specific biomarker, cTn still leaves important gaps. First, there is a 4–6 hours delay from symptom-onset to first appearance of measurable cTn in plasma. This often necessitates overnight stay for many patients to allow serial measurements before AMI can be reliably ruled out, thus increasing hospitalizations and health care costs [8]. The use of high-sensitivity cardiac troponin (hs-Tn), does offset this

delay to a certain degree, but at the cost of high false-positives. Second, prolonged elevation of plasma cTn (7–10 days) after an AMI complicates utility as a marker of early re-infarction. To address these gaps, a host of novel biomarkers—including structural proteins, enzymes of energy metabolism, inflammatory markers, cell-adhesion molecules, and extracellular matrix proteins have been investigated. More prominent among these include heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase isoenzyme-BB (GPBB), copeptin, and ischaemia-modified albumin, among others [9,10]. Among these, (H-FABP) is oldest known, and hence perhaps the most well-studied.

The current review aims to: (i) put in perspective the current literature comparing H-FABP to cTn and hs-Tn, (ii) offer insights as to whether H-FABP still has a role as a marker of myocardial injury in the current era of cTn, and if so, the population most suited for it, and (iii) briefly review some emerging, non-ACS indications for H-FABP use.

## Tissue distribution and plasma kinetics of H-FABP

Fatty acid-binding proteins (FABP) are members of the lipid-binding proteins superfamily. They are both membrane-bound – aiding cellular long-chain fatty acid (FA) uptake – and cytoplasmic, being crucial to intracellular transport of FAs to sites of metabolic conversion. Hence, FABPs are ubiquitous, though especially abundant in tissues with an active FA metabolism, including heart, kidneys, brain, and mammary glands, among others [11]. Among nine tissue-specific cytoplasmic FABPs identified so far, FABP-3 is predominantly distributed in cardiac myocytes and is also named heart-type fatty acid-binding protein (H-FABP) [12]. However, the myocardial tissue-specificity of H-FABP is not absolute, significant amounts being present in skeletal muscle, kidneys, mammary glands, testes, lungs and stomach [13,14].

Plasma kinetics of H-FABP reflects small size (15 kDa), and abundant existence in freely soluble form in the cardiomyocyte cytoplasm, in contrast to cTn, which is largely bound to the contractile elements of the cardiomyocyte. Hence, significant myocardial injury or even necrosis has to occur before cTn is released into the plasma in quantities detectable by standard assays. The abundance and freely soluble cytoplasmic location of H-FABP are evidenced by the fact that plasma H-FABP concentrations in response to myocardial injury rise to >100 times the plasma concentration of cTn, hence the normal cut-off of 5–7 ng/l

ml versus ≈0.05 for the latter (Tables 1 and 2). Whilst CK-MB and cTn are undetectable for around 4–6 h after symptom-onset, peak at around 12 h, and return to baseline at 24–72 h and 7–10 days, respectively [39], plasma H-FABP levels start rising within one hour, peak at 4–6 h, and return to baseline around 24 h after myocardial injury, owing to rapid renal clearance [40,41]. The distinct plasma kinetic profile offers two theoretical advantages, i.e. (i) enhanced utility as an earlier biomarker of AMI, and (ii) utility as a marker of re-infarction. Moreover, given the predominant presence in soluble form, even minor myocardial ischaemia and injury should cause detectable plasma elevations of H-FABP. Hence, beyond aiding early diagnosis of AMI, H-FABP may help identify troponin-negative high-risk patients with CP, and hence refine risk-stratification of such patients.

## H-FABP versus cTn as biomarker of AMI

### *H-FABP versus cTn: sensitivity, specificity and accuracy*

First recognised as a potential marker of myocardial damage in the late 1980s–early 1990s [40,42,43], the following decade saw H-FABP easily surpassing the legacy markers (CK-MB and myoglobin), especially early after symptom onset [44,45]. However, the rapid development of cTn assays in the late 1990s, after demonstration of excellent sensitivity and specificity in the eventual diagnosis of AMI, led to the adoption of cTn in the universal definition of AMI in 2000, and relegated H-FABP to the background.

Early comparisons between H-FABP and cTn, before the latter became part of universal definition of AMI, revealed H-FABP far exceeding the sensitivity of cTn, especially in those presenting ≤3-hours of symptom-onset in both high-risk and low-risk cohorts [15–17]. Notably, using cTn to define AMI led to a decrease in H-FABP's sensitivity and an increase in that of cTn, though the former remained significantly better [16]. As noted in Table 1, there is significant heterogeneity in findings across studies, likely due to small sample sizes, different cut-off values, specific cTn and H-FABP assays used, population characteristics, definition of end-points (AMI versus ACS), and time to symptom-onset, among others. Nevertheless, there is certainly consistency regarding the superior sensitivity of H-FABP over cTn, especially early after symptom-onset, with cTn catching up or exceeding H-FABP after about hour 4–6. On the other hand, cTn remains more specific at all times. Consolidating the evidence, several meta-analyses have confirmed a higher sensitivity for

**Table 1.** Comparative sensitivity and specificity of HFABP versus troponin by time of symptom onset in evaluation of acute chest pain.

First author, year. (End-point)	Population (N)	Plasma cut-off (ng/ml)			HFABP			Tn			HFABP + Tn		
		Tn	HFABP	s/s onset	Sens. (NPV) %	Spec. (PPV) %	AUC	Sens. (NPV) %	Spec. (PPV) %	AUC	Sens. (NPV) %	Spec. (PPV) %	
Hastrup, 2000 [15]	Typical CP (130)	0.5	8	2.3 (0–6) h	76 (95)	83 (46)	NR	33 (88)	96 (64)	NR	NR	NR	
	1.0	12	76 (95)	96 (80)	19 (86)	98 (67)		19 (86)	98 (67)				
	2.0	15	62 (93)	97 (81)	19 (86)	99 (80)		22 (50)	94 (80)				
	NR (TnT)	6.2	<2h	89 (80)	52 (69)	0.72		22 (50)	94 (80)				
Seino, 2003 [16] (AMI)	NSTEMI = 12.3% CP + Non-diagnostic EKG (371) AMI = 49%			2–4h	96 (91)	45 (68)	0.84	57 (65)	70 (91)				
				4–6h	100 (100)	40 (57)	0.96	67 (71)	66 (61)				
				6–12h	97 (97)	55 (55)	NR	94 (95)	68 (62)				
				12–24h	95 (90)	53 (70)	NR	95 (92)	65 (76)				
Seino, 2004 [17] (AMI)	CP+1ST or ↑Tn (129) AMI = 24%	NR (TnT)	6.2	<3h	100 (100)	63 (44.4)	NR	50 (86.7)	96.3 (80)	NR	NR	NR	
				3–6h	75 (93.8)	93.8 (75)	0 (78.9)	93.8 (0)					
				6–12h	100 (100)	72.7 (62.5)	60 (84.6)	100 (100)					
				>12h	100 (100)	75 (62.5)	100 (100)	87.5 (76)					
Ruzgar, 2006 [18] (ACS)	Patients with ACS (40) STEMI = 52%	0.01 (TnT)	6.2	<6h	95.2	100	NR	38.1	100	NR	NR	NR	
	NSTEMI= 30%			6–24h	91	100	100	100	100				
Cavus, 2006 [19] (ACS)	Typical CP < 1 hour (67) STEMI = 27%	0.1 (TnT)	7	<1h	97.6	38.5	NR	100	23.1	NR	NR	NR	
McCann, 2008 [20] (AMI)	NSTEMI = 10% Ischaemic CP (415) STEMI = 18%	0.03 (TnT)	5	<4h	73 (73)	71 (71)	0.77	55 (68)	95 (92)	0.78	85 (83)	69 (73)	
	NSTEMI = 30%			≥4h	78 (75)	56 (61)	0.74 (all)	88 (90)	94 (92)	0.88 (all)	98 (97)	55 (66)	
Valle, 2008 [21] (AMI+ACs)	Suspected ACS (419)	NR (TnT)	7	74±51 min	60 (80)	88 (72)	NR	19 (69)	99 (97)	NR	NR	NR	
Orak, 2010 [22] (ACS)	AMI = 35% Sudden CP + dyspnea/syncope/nausea / vomiting <6h duration (83) STEMI = 58%	0.01 (TnI)	2	<3h	100	75	0.967 (<6h)	100	20	0.556	NR	NR	
				3–6h (all)	97	68	75	21	21	(<6 h)			
				<6 h (all)	98	71	77	20	20				
Haltern, 2010 [23] (AMI)	Ischaemic-type CP (94) STEMI = 12% NSTEMI = 16%	0.03 (TnT)	7.3	<4h	86 (92)	66 (50)	0.76 (<4h)	42 (81)	100 (100)	0.71(<4h)	93 (96)	66 (52)	
	CP suggesting AMI (117)			>4h	59 (72)	64 (50)	0.71 (all)	100 (100)	100 (100)	0.87(all)	100 (100)	64 (63)	
Kim, 2010 [24] (AMI)	AMI-55%	0.1 (TnT)	19	<2h	60	77.4 (all)	0.78 (all)	20.2	98.1 (all)	0.82 (all)	33.3	NR	
				2–4h	64.7	91.7	58.3	17.7			82.4	NR	
				4–6h	88.9	66.7					91.7	NR	
McMahon, 2012 [25] (AMI)	CP considered cardiac (1128) AMI = 10%	0.37 (TnI)	5.24	<3h	64.3 (93)	84.2 (43)	0.84	50 (92)	93.3 (60)	0.76	71.4 (94)		
				3–6h	85.3 (97)	88.7 (55)	0.89	67.6 (95)	94.3 (66)	0.85	88.2 (98)		
				6–12h	89.9 (98)	93.5 (70)	0.94	81 (97)	94.2 (70)	0.90	92.4 (99)		
				12–24h	90.1 (99)	91.4 (56)	0.97	95.8 (99)	94.3 (71)	0.98	NR (100)		
Garcia-Valdecasas, 2011 [26] (AMI)	Ischaemic CP within 6h (165) AMI = 40% CP s/o AMI w/o STEMI	0.6 (TnI)	6.2	<3h	81 (82)	53 (52)	0.73	6 (61)	98 (67)	0.66	NR	NR	
Aldous, 2012 [27] (AMI)	NSTEMI = 15.6%	0.028 (TnI)	60	<6h	81 (80)	50 (52)	0.72	25 (65)	91 (64)	0.66	86.7 (97.2)	87 (55.3)	
Gerede, 2015 [28] (AMI)	Ischaemic-type CP >30 min duration (48)	0.04 (TnI)	7	<3h	89 (86)	100 (100)	NR	33 (50)	100 (100)	NR	NR	NR	
	NSTEMI = 50%			3–6h	70 (73)	89(88)		70 (67)	67 (70)				
Vuppurturi, 2015 [29] (AMI)	CP suggestive of ischaemia (77) AMI > 50%	0.14 (TnI)	6.4	>6h	100 (100)	89 (83)	NR	100 (100)	89 (83)	NR	NR	NR	
				≤6h	100 (100)	85.7 (88.2)		100 (100)	90 (100)				
				>6h	78.6 (62.5)	45.5 (64.7)		78.6 (78.6)	100 (100)				

Time to symptom onset reported as Mean (SD) or Median (IQR), as applicable. NPV and PPV were calculated in case of Seino 2003 using published raw data.

AM: Acute myocardial infarction; ACS: acute coronary syndrome; CP: chest pain; NSTEMI: non ST-elevation myocardial infarction; s/o-symptoms of STEMI: ST-elevation myocardial infarction; NR: not reported.

H-FABP in early diagnosis of AMI, though at the cost of a lower specificity [46–48]. Combining the two markers improved sensitivity, albeit at the cost of even lower specificity [47,48]. The better sensitivity and lower specificity of H-FABP translates to a similar or only marginally better overall test accuracy over cTn in most reports. Of note, almost all investigations after 2004 use cTn elevation to define AMI, making it difficult and perhaps impossible for a novel marker to exceed cTn in test accuracy, and more importantly, likely underestimating the true sensitivity of H-FABP.

### ***H-FABP versus cTn: predictive values and role of population characteristics***

Though sensitivity, specificity, and receiver operating characteristics-area under the curve (ROC-AUC) are useful measures of a test's fundamental credentials when compared to a "gold standard", they are little help in guiding clinical decisions. To that end, negative and positive predictive values (NPV and PPV respectively) are much more relevant, since they directly depict the probability of a negative or positive test indicating the absence or presence of a disease, respectively [49]. In the report by McCann et al., for example, H-FABP had a NPV of 73% in 415 patients presenting within 4-hours of symptom-onset, given an AMI prevalence of 50% [20]. Changing prevalence to a more realistic 5%, while keeping sensitivity and specificity unchanged, the NPV of H-FABP increases to 98.5%. Even a conservative 10% prevalence yields an NPV of 95.5%.

To demonstrate this more clearly, we extracted raw data of AMI prevalence, time to symptom-onset, and H-FABP test characteristics from reports in Tables 1 and 2. To study whether, and to what extent the first two could explain the observed heterogeneity in NPV among these reports, we regressed AMI prevalence (independent variable) against overall NPV of H-FABP(dependent variable) using the Analyze-it Tool Pak in Microsoft Excel 2016. As expected, there was a moderate correlation ( $R=-0.55$ ,  $p=.0003$ ) between AMI prevalence and NPV (Figure 1, upper panel), with prevalence accounting for  $\approx 1/3$  ( $R^2=0.3042$ ) of the variability in NPV. Obviously, given the rapid rise and decline of H-FABP, time from symptom-onset should also influence NPV. To isolate the effects of time and AMI prevalence, Figure 1 (lower panel) displays the relation between prevalence of AMI and NPV only among early presenters (<3–4 h), this time revealing an even stronger correlation between the two ( $R=$

$-0.60$ ,  $p=.01$ ), with prevalence accounting for over one-third the variability in reported NPVs ( $R^2=0.36$ ).

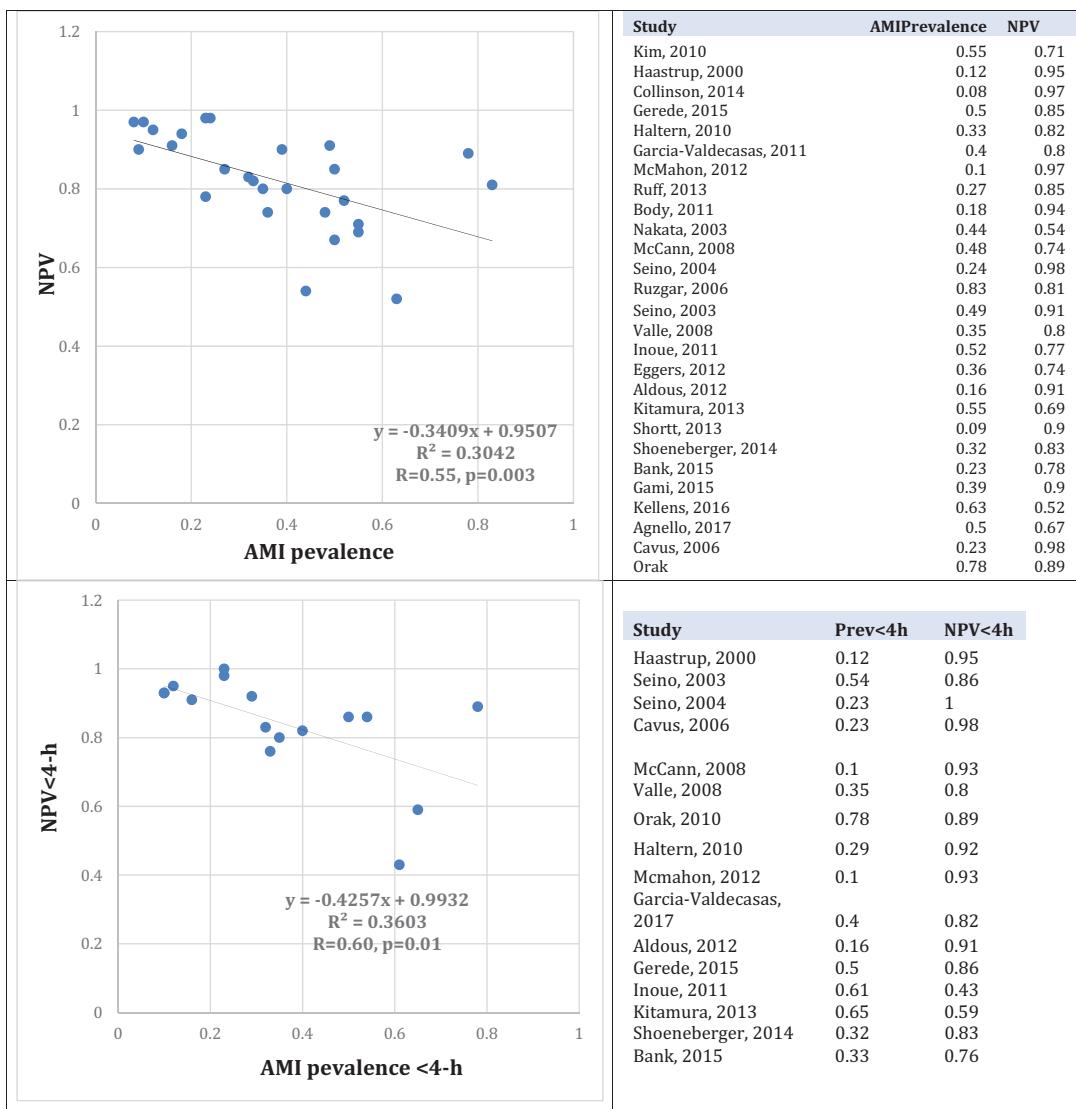
It should be noted that since most reports did not report AMI prevalence in each time from symptom onset sub-group, we assumed that AMI prevalence in each sub-group was not significantly different from the overall prevalence. Though a possible source of error, we believe that the prevalence of AMI among early presenters should indeed be higher than late presenters. Hence our assumption, even if erroneous, should result in an error on the conservative side, i.e. underestimate the correlation between the two variables rather than overestimate it. Put another way, using the same raw data, Figure 2 depicts the effect of changing AMI prevalence to 10% on NPV among early presenters, keeping sensitivity and specificity unchanged. We again assumed a similar AMI prevalence between early presenters and the entire. As expected, NPV uniformly increases markedly in each case. Much more importantly, heterogeneity among these reports almost disappears, revealing an NPV of >95% consistently across reports.

### ***H-FABP is most suited to rule out AMI in low-risk early presenters***

The clear association between AMI prevalence and NPV, as well as the impact of a "real-world" prevalence of AMI on NPV of H-FABP, as suggested by Figures 1 and 2, respectively, offer clues regarding causes of heterogeneity in the literature, while aiding clinical application of H-FABP. Indeed, H-FABP may be best suited for ruling out AMI in low-risk patients presenting early after CP onset (<4 h).

Directly supporting this, a few large cohorts with AMI prevalence  $\leq 10\%$  have consistently found very high NPVs for H-FABP [25,50]. McMahon et al. reported an NPV of 93% for H-FABP versus 92% for cTn in a large cohort with an AMI prevalence of 10% among those presenting within 3-hours of symptom-onset [25]. In the RATPAC trial, a low-risk (8% ACS prevalence) cohort of 850 patients presenting to the ED at a median 220 min after symptom onset, admission H-FABP had an NPV of 97% versus 98% for cTn [50]. However, NPV for the early presenter ( $\leq 3$  h) cohort was not reported by the RATPAC authors, neither was raw data available to allow calculation of NPV for this sub-group.

Hence, when applied to a more real-world population and early presenters, H-FABP does indeed seem to consistently show a very high NPV, providing a potential tool to "rule out" AMI during the early



**Figure 1.** Correlation between AMI prevalence and negative predictive value overall (upper panel), and among those presenting <4-h after symptom-onset (lower panel).

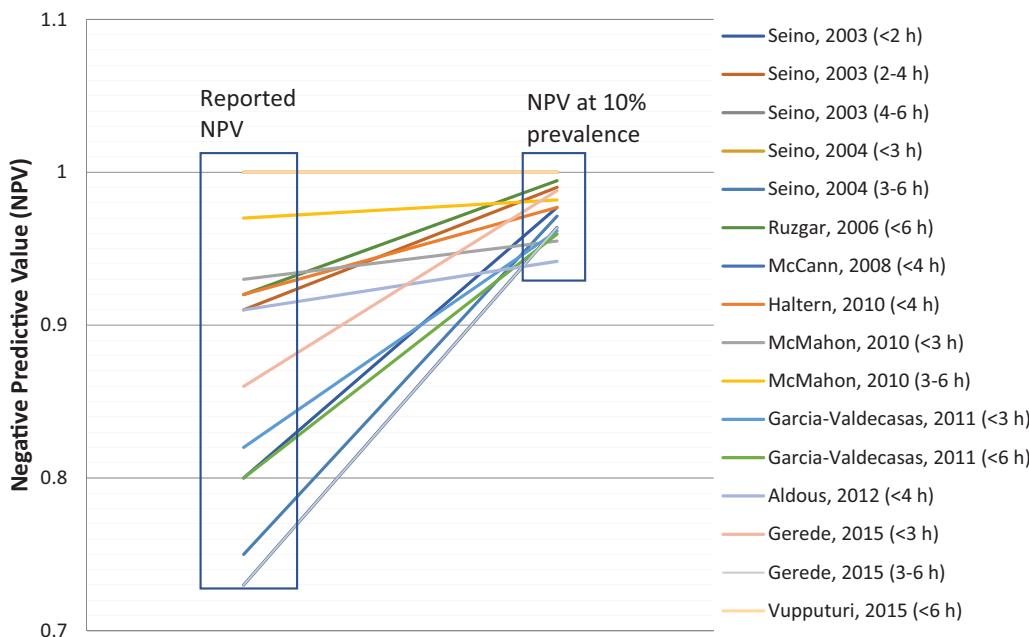
window of cTn-negativity. To put this in further perspective, a clinically acceptable marker should not exceed the current “accepted” rate of missed AMI, i.e. 1–2%, dictating the need for an NPV  $\geq 98\%$  [51]. In this regard, Body et al. reported an NPV of 98.8% when H-FABP and cTn were combined in clinically low-risk patients, enabling AMI to be ruled out at presentation in  $\approx 45\%$  of all patients, at the cost 6 AMIs missed per 1000 patients, a miss rate of 0.6% [52].

Finally, given the staggered time course of the two markers’ rise in plasma, combining them may aid in better assessing the onset time of ischaemia. Hence, patients with an uncertain time of symptom-onset, a positive H-FABP with a normal cTn will likely mean duration of symptoms of 0–4 h, whereas a normal H-FABP with elevated cTn would indicate the ischaemic event having occurred  $>24$  h previously. Such

knowledge/assessment could have important implications on individualising treatment strategies.

On the other hand, the specificity and PPV of H-FABP is consistently lower than cTn, regardless of time from symptom-onset. Given the high prevalence of AMI in populations studied, PPV can only be expected to be much lower in a real-world population, making it largely unsuited, or at the very least inferior to c-Tn for confirming AMI, patients deemed high risk based on history and/or EKG. This low specificity is likely multi-factorial, including known elevations of H-FABP in those with renal disease, skeletal muscle disorders/trauma, and myocardial injury of diverse aetiologies like heart failure, pulmonary embolism (see later), etc.

Finally, two other factors need to be considered when interpreting extant evidence. Firstly, using the comparator biomarker (cTn) itself as the diagnostic



**Figure 2.** Reported NPV and NPV if prevalence of AMI in each report were to be 10%. NPV at 10% prevalence calculated using the formula:  $NPV = \frac{(specificity * (1-prevalence))}{[(specificity * (1-prevalence)) + ((1-sensitivity)* prevalence)]}$ . Raw data of AMI prevalence and NPV were obtained from studies in Table 1.

gold standard for the outcome (AMI) being studied, as has been the case in the majority of reports in the last two decades is flawed. Intuitively, test characteristics of cTn will have a direct influence on the test characteristics of H-FABP, independent of all other factors. In particular, low specificity of cTn will impact the sensitivity of H-FABP, since some false-positives (due to low specificity) on cTn-testing will be erroneously deemed false-negatives (hence lower sensitivity) on H-FABP-testing. Indeed, Seino et al. found a decline of H-FABP's sensitivity by about 5–10% for all time points after symptom-onset [16], and a recent meta-analysis reported H-FABP having a sensitivity of 76% when cTn was used to diagnose AMI, versus 91% otherwise [46].

The second issue pertains to the relative assay quality of the two markers. Given that cTn has become the standard of care, and in fact now defines AMI, there is obviously a greater commercial interest in advancing cTn assays, rather than a novel test that bears significantly greater burden of evidence to bring. As a result, cTn assays have constantly improved in sensitivity and precision, while H-FABP assays have seen little change [53]. Indeed, most studies use point-of-care, semi-quantitative H-FABP assays, which detect either normal or elevated H-FABP above a cut-off set at  $\approx 6\text{ng/ml}$ . This is problematic since such tests may suffer inert-observer variability in result interpretation (usually colour development), as well as the inherent inability to distinguish moderate from high levels of

the marker. Even with these early generation assays, H-FABP has proven to be equally sensitive as even the latest generation hs-Tn. Hopefully, novel, highly sensitive and precise H-FFABP assays will aid this marker to realise its full promise.

#### ***H-FABP vs cTn diagnosis and prognosis of unstable angina (UA)***

UA and NSTEMI represent a continuum, with the boundary between them constantly changing as precision and sensitivity of biomarkers has advanced. In essence, many patients who were classified as UA in the era of CK/CK-MB, are now classified as NSTEMI, due to the much higher sensitivity of cTn. Biomarker release likely begins even with minor myocardial injury, but may not cross the assay threshold or diagnostic cut-off. A soluble marker like H-FABP rises early and to a greater degree than a structurally bound marker like cTn, the latter requiring significant necrosis before release. Given the continuum of severity and amount of myocardial injury in patients with UA, some patients will have enough biomarker leak to cross the detection threshold of an assay, while some may not. This would especially be true of semi-quantitative assays as have mostly been used for H-FABP.

Seino et al. found admission H-FABP elevated in 24/51 patients with UA (14/51 had elevated cTn), whereas Cavus et al. found admission and 4-hour H-FABP

elevated in only 1/42 patients with UA [16,19]. Compared to hs-Tn, Eggers et al. found mean admission H-FABP levels not significantly different from those without ACS, whereas mean hs-Tn levels were, though even the latter were elevated in only 18/68 patients with UA [31]. Besides being generally small in size, each of these reports had differing definitions of UA, and variable proportions of patients with confounding illnesses, like renal failure, heart failure, tachy-arrhythmias, etc. Valle et al. found the sensitivity/NPV of H-FABP to fall from 60%/80% to 47%/56%, respectively, when ACS (AMI + UA) was used as outcomes versus AMI [21]. Only 24.4% of patients with UA had elevated H-FABP versus 13.2% for cTn. However, this is controversial, as according to the universal definition of AMI, any significant rise in cardiac enzymes would class the definition as NSTEMI rather than UA.

Regardless of these barriers, H-FABP has repeatedly been demonstrated to have prognostic value incrementally to-and indeed independent of cTn among patients presenting to the ED with ACS (see below). Though lacking direct evidence of its role in UA, largely due to inherent issues with the clinical entity itself, the enhanced prognostic ability of H-FABP likely stems from its ability to identify patients with minor myocardial injury. Definitive evidence of this would require large prospective studies excluding patients with any co-existent confounding co-morbidities, like heart failure, renal disease, tachy-arrhythmias, myopericarditis, etc. Indeed, maybe exquisitely sensitive markers like H-FABP, or for that matter hs-Tn, could be used to define UA when cTn is normal. Again, large scale studies to determine cut-offs for normality, and the development of high-precision assays are both fundamental to achieving this.

### **H-FABP in the era of high-sensitivity troponin (hs-Tn)**

The last decade has seen significant improvements in cTn assays, with current generation “highly-sensitive” troponin (hs-Tn) assays able to detect very low concentrations of cTn in the plasma. In general, these assays have <10% coefficient of variation at plasma concentrations that are an order of magnitude lower than conventional cTn assays. Although largely structurally bound to the myocyte contractile elements, about 5% of cTn is present in free form in the cytoplasm [54]. Akin to H-FABP, this cytoplasmic cTn is released early after onset of ischaemic injury, but falls below the detection limit of conventional assays.

Hence, hs-Tn assays, by detecting this minuscule rise early after symptom-onset have proven more sensitive than cTn, and displayed very high NPVs [55–57]. Obviously, this increased sensitivity comes at the cost of poorer specificity. Intuitively, it follows that the major improvement of hs-Tn over cTn lies largely in rapidly “ruling out”, rather than “ruling in” AMI. Therefore, hs-Tn has a role very analogous to H-FABP, i.e. shortening the window of cTn-negativity.

In one of the earliest reports of hs-Tn, H-FABP was noted to be the only biomarker among several to have equivalent diagnostic accuracy as hs-Tn in those with CP onset <3-hours, and superior to hs-Tn in those with onset <2 h [56]. Several investigations since have compared the two markers, especially early after symptom onset (Table 2). Importantly, the hs-Tn assay itself has evolved rapidly since being introduced, making it difficult to compare earlier reports to more recent ones. As with the c-Tn studies, most reports have a very high AMI prevalence. Nevertheless, and especially in more recent reports, using the latest-generation assays, hs-Tn has generally demonstrated superior sensitivity and NPV compared to H-FABP, even early after symptom onset. This increased sensitivity, however, comes at a cost of lower specificity. Overall test accuracy, as measured by the ROC-AUC, seems largely equivalent between the two markers.

In the largest cohort to date, the APACE study enrolled 1074 consecutive patients with CP suggestive of AMI [58]. H-FABP had a lower ROC-AUC than hs-Tn in the overall cohort (0.84 vs 0.94), and in those presenting <3-hours from symptom-onset (0.85 vs 0.92). Combining the two markers yielded an even lower accuracy than hs-Tn alone (ROC-AUC 0.88 vs 0.92). However, both H-FABP and hs-Tn had very high NPV (94% vs 98%, respectively), and poor PPV (41% vs 42%) with an AMI prevalence of 20%. Similar findings were reported by Collinson et al. in another large cohort of 850 low-risk patients presenting early to the ED with CP [50]. Meta-analyses seem to confirm the higher sensitivity of hs-Tn, and the relative lack of improvement with H-FABP [59,60]. However, there was significant heterogeneity among studies, and early presenters (<3–4 h from symptom-onset) – the real target population for both markers – were largely missing in both analyses, still leaving questions about the utility of H-FABP in the era of hs-Tn.

To help put these findings in a clinical context, a novel risk scoring system, the Manchester Acute Coronary Syndromes Rule (MACS), incorporating both hs-Tn and H-FABP levels, along with clinical features and EKG was developed and validated [61,62]. A

**Table 2.** Test characteristics of H-FABP versus hs-Tn in those presenting to ED with CP, stratified by time to symptom onset.

First author, Year	Population (N), prevalence of AMI	Plasma cut-off (ng/ml)		Time to s/s		H-FABP		hs-Tn		hs-Tn + H-FABP		
		hs-Tn	H-FABP	Sens. (NPV)	AUC	Sens. (NPV)	Spec.(PPV)	AUC	Sens. (NPV)	Spec.(PPV)	AUC	Sens. (NPV)
Inoue, 2011 [30] (ACS)	CP > 20 min (432) STEMI = 52% NSTEMI = 9%	0.014 (hs-TnT)	6.2	<2 h <3 h <4 h <6 h <4 h <8 h <4 h	79 (42) 73 (41) 76 (43) 80 (49) 28.6 39.1 (73.8) 50 (90.7)	66 (87) 61 (87) 73 (93) 65 (88) 0.74 0.80 (94.8) 0.89 (47.6)	0.70 0.69 0.74 0.74 0.74 0.80 0.90 (97.6)	72 (40) 77 (38) 83 (44) 85 (52) 73.5 78.9 (86.5) 79.6 (45)	57 (84) 48 (83) 52 (86) 57 (86) 0.68 74.6 (63.1) 79.7 (86.9)	NR	0.67 0.72 0.72 0.72 0.84 90 (97.5) 90 (97.5)	NR
Eggers, 2012 [31] (AMI)	CP + no STEMI (360) NSTEMI = 35.6% CP s/o AMI, no STEMI (384)	0.014 (hs-TnT)	5.8	<4 h <8 h <4 h	38 (57) 88 (67) 50 (84)	94.8 (94.8) 75 (92) 100 (100)	0.80 0.95 0.81	74.6 (63.1) 75 (93) 100 (100)	0.84 0.94 0.96	NR	74.6 (63.4) 73.5 (38.6)	
Aldous, 2012 [27] (AMI)	NSTEMI = 15.6% S/s suggestive of AMI (85)	0.014 (hs-TnT)	6	<2 h >4 h >6 h	38 (57) 88 (67) 43 (90)	93 (86) 75 (92) 80 (24)	0.70 0.95 0.81	25 (40) 100 (100) 86 (97)	57 (40) 81 (67) 63 (25)	0.48 0.94 0.96	NR	
Kitamura, 2013 [32] (AMI)	NSTEMI = 12% STEMI = 43% Possible ACS s/s < 6 h (163)	0.014 (hs-TnT)	6.2	<2 h >4 h >6 h	5.2	58.8 (83.3)	0.84	70.6 (85.9)	85.9 (70.6)	0.88	NR	
Shortt, 2013 [33] (AMI)	AMI = 8.6% CP s/o AMI (105) AMI = 32.4%	5.76	<1 h								NR	
Shoenenberger, 2014 [34] (AMI)	CP s/o ACS, no STEMI (453)	0.014 (hs-TnT)	7	<3 h 3–6 h >6 h	47 (76) 68 (89) 59 (77)	85 (61) 79 (50) 77 (59)	0.73 0.78 0.73	63 (83) 64 (89) 87 (92)	92 (81) 89 (64) 92 (80)	0.86 0.86 0.91	83 (68) 79 (59) 72 (64)	
Bank, 2015 [35] (ACS)	NSTEMI = 23% CP <6 h (88)	0.014 (hs-TnT)	5	<6 h	85 (90)	88 (82)	0.89	94 (94)	62 (61)	0.8	100 (100)	
Gami, 2015 [36] (AMI)	AMI = 38.6% Typical CP (152)	(hs-TnT)	5.3	158 min (median)	54 (52)	84 (85)	0.79	72 (61)	73 (82)	0.83	82 (70)	
Kellens, 2016 [37] (AMI)	NSTEMI = 33% CP < 1-h duration + normal cTn (n = 28 CP + 28 controls)	6.1	<1 hour	55.5 (67)	89.2 (83)	0.65	34 (60.4)	100 (100)	0.80	NR	NR	
Agnello, 2017 [38]												

ACS: Acute Coronary Syndrome; AMI: Acute myocardial infarction; CP: Chest pain; NSTEMI: Non ST-Elevation Myocardial Infarction; S/o: Symptoms of; STEMI: ST-Elevation Myocardial Infarction; NR: Not Reported.  
Data from Inoue et al. was extracted from graphs using the online graph reader tool ([www.graphreader.com](http://www.graphreader.com)).

recent pilot RCT found that the MACS rule enabled 26% patients to be successfully discharged from the ED within 4 h with no incident AMI in 30 days among those discharged [63]. Similarly, an analysis of a single-center arm of the multi-center ADAPT study found that when combined with EKG, H-FABP or hs-Tn alone had unacceptably low sensitivity [64]. However, in combination H-FABP + hs-Tn + EKG changes maximised rule-outs ( $\approx$ 41% testing negative) while maintaining >99% sensitivity. Other authors have also demonstrated the benefits of this combination approach [65].

To summarise, H-FABP may yet prove to be an important adjunct to hs-Tn, enabling an optimal balance between sensitivity (and NPV) and specificity (and PPV). Current evidence suggests that hs-Tn + H-FABP combination strategy would maximize safe discharges while minimising missed AMIs. Obviously, adequately powered RCTs examining the optimised cut-off values and timing in relation to symptom-onset are needed.

### **Prognostic value of H-FABP in patients with ACS**

Since H-FABP may be released into the plasma following myocardial injury even without myocardial necrosis, the prognostic value of H-FABP in those with suspected ACS has been extensively studied, to identify cTn-negative patients who may be high risk, and hence warrant observation or diagnostic workup.

Ishii et al. first reported that in 328 consecutive patients with ACS (47% STEMI, 26.5% UA/NSTEMI), serum H-FABP  $>$  9.8 ng/mL in first 6 h after CP onset, but not elevated cTn, was a strong predictor of cardiac death and non-fatal AMI within 6 months [66]. Several subsequent reports have consistently demonstrated superiority of H-FABP over c-Tn, and indeed other biomarkers in this regard (Table 3). Viswanathan et al. tested the prognostic value of H-FABP against hs-Tn for the first time, and in a lower risk population than prior studies (AMI prevalence 20.8%, STEMI excluded) [72]. Of note, both were measured in the plasma  $>$  12 h after symptom onset. Even so, H-FABP predicted death or AMI within 18 months independent of hs-Tn levels across the entire cohort. More importantly, H-FABP  $>$  6.48 ng/ml strongly predicted 18-month death and AMI in hs-Tn-negative patients, proving generalizability of previous findings to a more "real world" cohort of unselected patients. Hence, H-FABP levels during the first hours after symptom onset have consistently been proven to identify a high-risk

population, regardless of cTn (or indeed hs-Tn) levels. RCTs comparing outcomes using treatment/diagnostic algorithms based on H-FABP, either alone or as part of a multiple biomarker strategy, are needed to facilitate adoption in clinical practice.

### **H-FABP in non-ACS disorders**

Given the prognostic ability of H-FABP in ACS (Table 3), its utility to identify high-risk patients in other non-ACS disorders known to cause myocardial strain, and perhaps injury in severe cases, has attracted attention.

#### **H-FABP in congestive heart failure (CHF)**

Cardiac biomarkers have become integral to the management of CHF. Established and widely available biomarkers including brain natriuretic peptide (BNP) and N-terminal-pro-brain natriuretic peptide (NT-pro-BNP), are useful in diagnosis (to rule out heart failure) [73,74], ascertain prognosis [75,76], predict mortality or re-hospitalization [77–79], and possibly guide early lifestyle and pharmacologic interventions in asymptomatic at-risk patients [80,81].

There seems to be little added value or improvement with H-FABP over natriuretic peptides in confirming the diagnosis of CHF. A *post hoc* analysis of the MANPRO cohort reported that H-FABP levels correlated with CHF clinical severity, and with echocardiographic indices of systolic and diastolic dysfunction [82]. However, though H-FABP plus NT-proBNP had a significant improvement in PPV compared to NT-proBNP alone (58% vs 45%,  $p < 0.0001$ ), it was well short of being recommended for clinical use. There was no improvement in NPV over NT-proBNP alone. Importantly, almost 25% patients in the "no acute CHF" group had a history of chronic CHF, making it difficult to interpret findings since H-FABP and NT-proBNP are known to be raised in those with chronic stable CHF, each to a variable degree. More recently, Lichtenauer et al., in a cohort of 124 patients with systolic CHF (ischaemic and non-ischaemic), showed H-FABP as having the highest AUC (0.80, 95% CI = 0.74–0.86) among several novel inflammatory markers, though no comparison to natriuretic peptides was performed [83].

Majority of the studies investigating H-FABP in CHF have focussed on prognostic utility, both in acute decompensated and chronic stable CHF (Table 4). Notably, these reports span widely varying populations in terms of the degree of systolic dysfunction, aetiology of CHF, and clinical severity as assessed by

**Table 3.** Prognostic utility of H-FABP in patients with ACS.

First Author, Year	N	Population (Time of blood sampling)	Follow up	Primary outcome	Biomarkers	Findings
Ishii, 2005 [66]	328	ACS (<6-h after s/s onset)	6-mo	Cardiac death Cardiac events	H-FABP c-Tn	H-FABP predicted 6-month cardiac events (RR 8.92, 1.15–69.4) but not cTn.
Suzuki, 2005 [67]	90	ACS (Admission)	30-d	All-cause death Cardiac event	H-FABP Troponin T CK-MB	H-FABP predicted cardiac events at 30-days (RR 44.98, 1.48–1364.88) but not cTn or CK-MB
O'Donoghue, 2006 [68]	2,287	ACS (41 ± 20 h after s/s onset)	10-mo	All-cause death Nonfatal AMI New/worsening CHF	H-FABP cTn BNP Myoglobin	H-FABP predicted death (HR 4.1, 2.6–6.5), CHF (HR 4.5, 2.6–7.8), MI (HR 1.6, 1.0–2.5), or all (HR 2.6, 1.9–3.5) 10 months independent of cTn/BNP. H-FABP incremental to cTn/BNP for prognosis.
Kilcullen, 2007 [69]	1,448	ACS (12-24 h after s/s)	12-mo	All-cause death	H-FABP cTn	H-FABP ≥ 5.8 ng/ml predicted 1-yr mortality (HR 11.35, 2–64.34) in cTn-negative (UA) patients, as well in those with ↑ cTn (NSTEMI) (HR 3.11, 1.45–6.7).
Ilva, 2009 [70]	293	Suspected ACS (Median 4.7 h after s/s onset)	6-mo	All-cause death Recurrent MI	cTnI H-FABP	cTnI independently predicted 6-mo death + AMI (RR 3.02, 1.62–5.63) but not H-FABP.
McCann, 2009 [71]	550	Suspected ACS (Median 6 h after s/s onset)	12-mo	All-cause death Recurrent AMI	H-FABP cTn NT-pro-BNP hs-CRP MPO MMP-9 others	Admission H-FABP (OR 2.7, 1.1–6.4), admission NT-pro-BNP (OR 2.7, 1.4–5.2), and peak cTn (OR 3.6, 1.4–9.0) independently predicted 1-yr mortality. H-FABP, cTn, NT-pro-BNP had incremental prognostic value
Viswanathan, 2010 [72]	955	hs-Tn-negative suspected ACS (NR)	18-mo	All-cause death Recurrent AMI	H-FABP hs-Tn	H-FABP predicted 18-month death/MI in hs-Tn (-) patients incrementally when stratified by degree of H-FABP elevation.
Garcia-Valdecasas, 2011 [26]	165	Chest pain (<6 h after s/s onset)	6-mo	All-cause death Recurrent ACS/AMI Other cardiac events	cTnI H-FABP CK-MB	Increased H-FABP (HR 2.50, 1.31–4.80) and cTn (2.53, 1.19–5.38) independently predicted 6 month outcomes.
Reiter, 2013 [58]	955	Chest pain suggestive of MI (<12-h after onset/peak of symptoms)	12-mo	All-cause death	H-FABP Copeptin hs-Tn	H-FABP predicted 1-yr mortality irrespective of hs-Tn

New York Heart Association Classification (NYHA). As noted in **Table 4**, reports have consistently found H-FABP to be the only, or at the very least, best predictor of outcomes in those with chronic stable CHF, when compared to other commonly used biomarkers [84,90–92]. In the only prognostic study restricted to HFpEF, Kutsuzawa et al. found H-FABP to be the sole predictor of CV events among a host of clinical (age, NYHA class, hypertension, diabetes, renal function) and biochemical markers (BNP, cTn, hs-CRP) [91]. Physiologically, it may be that since BNP is a surrogate for myocardial “stretch” engendered by pressure/volume overload, while H-FABP directly depicts myocardial injury, the latter is a better predictor of adverse outcomes by virtue of indicating ongoing myocardial

damage. In a small study comparing hs-Tn, H-FABP and NT-proBNP between 49 patients with HFpEF, 51 patients with asymptomatic diastolic dysfunction, and 30 controls with normal diastolic function, all three markers were elevated in HFpEF, only hs-Tn and H-FABP were elevated in asymptomatic diastolic dysfunction, indicating that subtle myocardial injury precedes the development of CHF [96].

In acute decompensated CHF (**Table 4**), H-FABP has again been found to exceed BNP and NT-proBNP as a predictor of mortality and readmissions [89]. In fact, among admission and discharge BNP and H-FABP, only discharge H-FABP was found to predict cardiac death and CHF readmission [95]. Hence, the admission H-FABP, as well as the H-FABP response to therapy in

**Table 4.** Studies investigating prognostic value of H-FABP in acute decompensated CHF and chronic stable CHF.

First Author, Year	Population (n)	Primary outcome	Follow up	Biomarker	Risk estimate, 95% CI
Setsuta, 2002 [84]	Stable chronic CHF (56)	All-cause death CHF readmission	16 ± 12-mo	H-FABP cTn BNP ANP CK-MB	HR 2.6, 1.1–6.5 per 3.86ng/ml increase HR 7, 1.1–44 NS NS NS
Arimoto, 2005 [85]	Acute CHF (179)	Cardiac death CHF readmission	20-mo	H-FABP LDH CK	HR 7.39, p = 0.0065 NS NS
Niizaki, 2005 [86]	Acute CHF (186)	Cardiac death CHF readmission	534 ± 350 days	H-FABP BNP	HR 5.42, 2.20–13.32 HR 2.41, 1.02–5.73
Komamura, 2006 [87]	Chronic stable non-ischaemic DCM (92)	Cardiac death Heart transplant LV assist device	48 months	H-FABP BNP cTn	RR 7.5, 0.7–36.1 RR 10.9, 3.5–35.3 NS
Niizeki, 2007 [88]	Acute CHF (126)	Cardiac death CHF readmission	474 ± 328-days	H-FABP BNP cTn	HR 15.7, 3.8–64.5 HR 2.6, 0.87–7.8 NS
Niizeki, 2008 [89]	Acute CHF (113) (Admission + discharge)	Cardiac death CHF readmission	624 ± 299 days	H-FABP (at discharge) BNP (at discharge)	HR 5.7, 2–9.5 OR 4.62, 1.49–14.33 <sup>a</sup>
Setsuta, 2008 [90]	Chronic stable CHF (103)	All-cause death CHF readmission	28 ± 26 mo	H-FABP cTn	HR 2.24, 1.21–4.14 HR 1.95, 1.02–3.71
Kutsuzawa, 2012 [91]	Chronic CHF with preserved EF (151)	Cardiac death CHF readmission	694 (29–2000) days	H-FABP cTn BNP hs-CRP	HR 1.165, 1.034–1.314 NS NS NS
Hoffmann, 2015 [82]	Acute CHF (122)	All-cause death CHF readmission	5-yrs	H-FABP cTn NT-proBNP	ACM-NS CHF readmit-HR 1.07, 1.02–1.13 CHF readmit /ACM-NS CHF readmit/ACM-NS
Otaki, 2014 [92]	Chronic stable CHF ± AF (402)	All-cause death Cardiac death CHF readmission	643 days-AF 488 days-SR	H-FABP-AF HFABP-SR cTn-AF cTn-SR BNP-AF/SR	HR 1.57, 1.2–2 HR 1.28, 1.04–1.58 HR 1.4, 1.13, 1.74 NS NS
Shirakabe, 2015 [93]	CHF ± AKI admitted to ICU (NYHA III/IV)	All-cause death CHF readmission	90-days	H-FABP hs-Tn BNP	HR 5.1, 1.86–14.17 NS NS
Kadowaki, 2017 [94]	Acute CHF (322)	Cardiac death CHF readmission	534 (203–1014) days	H-FABP BNP	HR 1.745, 1.088–2.7903 NS
Kazimierczyk, 2018 [95]	Acute NYHA III/IV CHF (71) Admission + discharge	CV death CHF readmission	9.2 ± 7.3-mo	H-FABP (at discharge) BNP	(OR 1.3, 1.06–1.68) NS

Unless specified, risk estimates in last column are for composite end-point, and are those achieved after multi-variate analyses, including co-markers checked in each study.

<sup>a</sup>OR for Niizeki, 2008 calculated from reported raw data.

acute CHF assessed at the time of discharge, akin to similar findings with BNP, may indeed identify candidates for aggressive therapy and close follow-up.

In summary, H-FABP may be a robust prognostic marker, both in chronic stable CHF, in acute decompensated CHF and also HFpEF, and indeed seems superior to BNP, NT-proBNP, and cTn.

#### Low and intermediate risk pulmonary embolism

In-hospital and early mortality in acute PE varies widely depending on the severity at presentation [97]. Those with severe or “massive” PE, as indicated by hemodynamic instability, are clearly recommended to receive immediate mechanical or chemical thrombolysis [98]. However, optimal management of non-high-risk, hemodynamically stable patients has been somewhat challenging, since this sub-group itself varies

widely in terms of risk of adverse outcomes. In particular, identifying those with subclinical right ventricular strain or myocardial injury, a group with an intermediate mortality risk, has attracted much focus [99,100].

Recent guidelines recommend using a combination of clinical assessment, imaging evidence of right ventricular dysfunction (RVD), and biomarkers (cTn) to further stratify this group into low, intermediate-low and intermediate-high risk, with different management strategies for each group, i.e. home discharge with anti-coagulation, inpatient observation, or close monitoring and rescue reperfusion if needed, respectively [98]. The guidelines also opine that “the optimal, clinically most relevant combination (and cut-off levels) of clinical and biochemical predictors of early PE-related death remain to be determined, particularly about identifying

**Table 5.** Prognostic performance of H-FABP in low-intermediate risk acute PE.

First Author, Year	Sample size	Primary outcome	Biomarkers	Findings (Risk estimate, 95%CI)
Boscheri, 2010 [103]	101	All-cause mortality at 6-mo	H-FABP Troponin I	H-FABP alone predicted 30-day PE-related mortality (OR 37, 5–266).
Dellas, 2010 [104]	126	All-cause mortality at 30-days CPR Endotracheal intubation Catecholamine use	H-FABP cTnT NT-proBNP	H-FABP alone predicted 30-day composite outcome (OR 36.6, 4.3–308) H-FABP alone predicted long term (median 499 days) mortality (HR 4.5, 2.0–9.8)
Gul, 2012 [105]	61	All-cause mortality at 30-days	H-FABP Troponin I CK-MB	H-FABP alone predicted 30-day mortality (OR 7.27, 1.78–29.7)
Lankeit, 2013 [106]	257	30-day adverse outcome (death, catecholamine use, endotracheal intubation, CPR)	H-FABP cTn NY-pro-BNP	H-FABP (OR 6.79, 2.4–19.26) stronger predictor of 30-day adverse outcomes than cTn (OR 3.47, 1.21–9.90), or NT-proBNP (OR 3.79, 1.20–11.95)
Gul, 2014 [107]	80	IHM and 30-day mortality	H-FABP cTn	H-FABP alone predicted in-hospital (HR 6.63, 1.33–33.34) & 30-day mortality (HR 7.81, 1.59–38.34) Thrombolysis in patients with ↑ H-FABP did not improve outcomes.
Langer, 2016 [108]	161	All-cause mortality at 30-days	H-FABP CK-MB Troponin I	H-FABP (OR 27.1, 2.1–352.3) stronger predictor of 30-day mortality than CK-MB (OR 5.3, 1.3–23.3). cTn did not predict outcomes after adjusting for other variables.
Dellas, 2018 [109]	716	Death, Resuscitation, Intubation or Catecholamine use in 30 days	H-FABP sPESI Multidetector CT	H-FABP had incremental prognostic value in low risk (sPESI = 0) and intermediate-risk (sPESI ≥ 1 or RVD on MDCT) patients.

ACM: all cause mortality; CK-MB: creatinine kinase MB; IHM: in-hospital mortality; RVD: right ventricular dysfunction; sPESI: simplified pulmonary embolism severity index; MDCT: multidetector computed tomography; NT-proBNP: N-terminal pro b-type natriuretic protein.

possible candidates for reperfusion treatment among patients with intermediate-risk PE", hence the ongoing search for novel markers.

The role of H-FABP in PE was first demonstrated by Kaczynska et al. in 2006, in a prospective cohort of 77 patients, including 9 with massive, 43 with sub-massive, and 25 with non-massive PE [101]. Compared to cTn, NT-pro-BNP, and myoglobin, H-FABP emerged as the only predictor of 30-day PE-related as well as all-cause mortality. These findings were quickly replicated by Puls et al. the following year, in a cohort of 107 patients [102]. Again, H-FABP was superior to cTn or NT-proBNP even when 24-hour peak levels of the latter were considered, and had additional prognostic ability over echocardiographic assessment of RV dysfunction (Table 5) summarizes subsequent reports investigating the prognostic value of H-FABP alone and against other markers in sub-massive/normotensive PE, whereby H-FABP appears to be a strong marker of adverse clinical outcomes in this population. A meta-analysis of 9 studies including 1680 patients found that elevated H-FABP levels were associated with an increased risk of RVD (OR 2.57; 95% CI, 1.05–6.33), complicated clinical course (OR 17.67; 95% CI, 6.02–51.89), and 30-day PE-related mortality (OR, 32.94; 95% CI, 8.80–123.21) [110]. Compared to hs-Tn, brain natriuretic peptide (BNP), and N-terminal-proBNP (NT-pro-BNP), H-FABP was the strongest predictor

of short-term PE-related and all-cause mortality, and had the lowest negative likelihood ratio for mortality.

H-FABP was tested as part of the European Society of Cardiology (ESC) guidelines algorithm for risk-stratifying patients with acute PE [109]. In 271 patients assessed to be low-risk by the simplified PE severity index (sPESI), 30-day complication rate (death, catecholamine use, mechanical ventilation, resuscitation) was 1.1%; however, those with an elevated H-FABP had a 4.3% complication rate, compared with 0.4% for those with normal H-FABP, thereby achieving significantly enhanced precision over clinical assessment alone. Hence, H-FABP seems to be a promising biomarker for risk-stratifying low-intermediate risk patients with acute PE. From the standpoint of triaging patients for thrombolysis, one small observational study did not find a difference in 30-day mortality between H-FABP-positive patients who received thrombolysis versus those who did not [107], although interventional RCTs are awaited.

### Other conditions

In patients undergoing coronary artery bypass grafting (CABG), the slow rise and fall of traditional biomarkers like CK-MB and cTn makes them unsuitable to discriminate between early graft failure, on the one hand, and the expected myocardial injury resulting from the surgery itself or ischaemia-reperfusion injury on the

other. Consistent with its presence in freely soluble form in the cardiac myocellular cytoplasm, H-FABP has been repeatedly found to be the earliest marker (as early as 60–90 min post-operatively) to increase post-operatively after CABG, even excluding patients with post-operative AMI [111–113]. Not surprisingly, in a prospective cohort of 1298 patients undergoing CABG, H-FABP peaked earlier, and was superior to c-Tn and CK-MB as a predictor of long-term mortality and ventricular dysfunction [114]. Hence, H-FABP may be a marker of high-risk patients and predict the requirement of closer post-operative monitoring, or more aggressive application of strategies to reduce ischaemia-reperfusion injury.

Given known tissue distribution patterns, H-FABP was also thought to have potential value in diagnosis and prognostication in neurologic disorders, most prominently ischaemic stroke and traumatic brain injury (TBI). In the context of ischaemic stroke, a small pilot study in 2004 indicated H-FABP may be significantly more sensitive and specific than the hitherto most extensively studied markers, neuron-specific enolase and S100B [115]. H-FABP seems to peak  $\approx 3$  h after symptom onset and remain elevated for up to 5 days, and more importantly, peak H-FABP values correlated with the severity of neurological deficit at 10–12 days ( $r^2=0.49$ ), and functional outcomes at 90 days ( $r^2=0.56$ ) [116]. However, the relation between H-FABP levels and infarct volume was non-linear, with markedly elevated levels of H-FABP restricted to those with an infarct volume of  $>150$  ml [116]. Subsequent small cohorts, as well as a very recent meta-analysis indicate that though H-FABP as a single marker has modest diagnostic and prognostic value in acute ischaemic stroke, it falls short of clinical applicability, though it may add value as part of a biomarker panel [117–119]. Whether H-FABP alone, or as part of a biomarker panel, has value identifying late-presenting stroke patients who might benefit from thrombolysis remains to be investigated.

The major role of biomarkers in traumatic brain injury (TBI) pertains to their role in improving initial triage in those with clinically mild TBI in order to reduce the need for costly and potentially harmful (radiation exposure) neuroimaging. This is especially important since the incidence of clinically significant imaging abnormalities in this sub-group is quite low, and computed tomography (CT) imaging is overused in this context [120,121]. Hence, the ideal biomarker in this case should have a very high NPV, in order to reliably mitigate the need of CT imaging in clinically mild, low-risk TBI. A screening study examining 87

biomarkers in 110 patients with clinically mild TBI found a predictive model with 6 of the markers including H-FABP to have an NPV of 98.6%, though a PPV of just 60% [122]. In a larger cohort of 261 patients with mild TBI, both H-FABP and S100B displayed high sensitivity and NPV, but the former had a higher specificity (6% vs 29% with sensitivity set at 100%), though the improvement in specificity hardly made H-FABP a clinically usable positive predictor of CT findings [123]. Most recently a panel of 8 biomarkers in TBI of all severities identified H-FABP combined with two other markers to constitute the best biomarker panel in terms of sensitivity to predict CT abnormalities [124]. Sensitivity, specificity, and predictive values of all markers individually were found subpar for clinical use. Hence, H-FABP's role in predicting CT-negativity in those with mild TBI seems best suited as part of a panel of biomarkers, a field that remains rapidly evolving, given the large number of potential markers being investigated.

More recently, myocardial injury, as defined by an elevated cTn, has been found to predict severe coronavirus disease 2019 (COVID-19) in some reports, raising speculation as to the high incidence of myocarditis in these patients [125,126]. Intriguingly, though hardly surprising, a recent small cohort reported significantly higher H-FABP levels in those with severe versus non-severe COVID-19 infection [127].

## Conclusion

To summarise, H-FABP remains a biomarker of high interest, even in the era of highly sensitive troponin assays, particularly in the context of ruling out AMI in low-risk early presenters, allowing earlier discharge of such patients from the ED and reducing cost. Lack of specificity, as has been seen with other biomarkers obviously makes it unsuitable for confirming AMI, especially as the sole marker. Lack of data, lack of progress in improving assay kits, iii) paucity of studies incorporating H-FABP with or without cTn or hs-Tn as part of clinical decision pathways.

By virtue of the fact, it is elevated in many cardiovascular conditions, helps identify patients at higher risk of complications, similar to the hs-cTn. Enough evidence now exists to directly investigate outcome-oriented clinical decision-making algorithms incorporating H-FABP, for example, whether these patients warrant further inpatient observation or testing. Its role in other non-cardiac conditions are also being appreciated. Improvement in assays and more studies would help make clinicians more aware of its utility

and perhaps it would find its rightful place in management algorithms.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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# La proteína de unión a los ácidos grasos cardíaca (HFABP) está relacionada con la gravedad de la insuficiencia cardíaca y sus biomarcadores cardíacos conocidos

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## Resumen

**Objetivos:** Determinar las concentraciones de proteína de unión a los ácidos grasos cardíaca (HFABP) en pacientes con insuficiencia cardíaca con fracción de eyección reducida (ICFER) y su potencial valor pronóstico.

**Métodos:** Se determinaron las concentraciones circulantes de HFABP mediante un inmunoensayo quimioluminiscente automático en 25 voluntarios sanos y 60 pacientes con ICFer.

**Resultados:** Los pacientes con insuficiencia cardíaca (IC) presentaron concentraciones de HFABP significativamente mayores que los voluntarios sanos. Se observó una correlación significativa entre los niveles de HFABP, la clasificación de la New York Heart Association (NYHA), y las concentraciones de los biomarcadores de disfunción y remodelado cardíaco (NT-proBNP, FGF-23 y galectina-3). Las concentraciones de HFABP también mostraron valor predictivo de muerte cardiovascular, y su combinación con NT-proBNP podría ser sinérgica a la hora de evaluar el riesgo.

**Conclusiones:** Las concentraciones de HFABP están aumentadas en los pacientes con ICFer, se relacionan con el riesgo cardiovascular y podrían ayudar a los especialistas en el manejo de los pacientes.

**Palabras clave:** biomarcador; insuficiencia cardíaca; NT-proBNP; proteína de unión a los ácidos grasos cardíaca (HFABP); resultado; riesgo.

## Introducción

La insuficiencia cardíaca (IC) afecta a millones de personas en todo el mundo y está asociada a un mal pronóstico [1, 2]. Los péptidos natriuréticos, el péptido natriurético tipo B (BNP) y el pro-BNP amino-terminal (NT-proBNP), son biomarcadores habitualmente empleados en el diagnóstico y manejo de pacientes con IC [3, 4].

El hallazgo de nuevos biomarcadores procedentes de otras vías fisiopatológicas podría mejorar la estratificación del riesgo, el manejo de resultados y la selección de tratamiento para los pacientes con IC [1, 5, 6]. Por esta razón, se ha analizado el valor añadido de los biomarcadores relacionados con el remodelado y la fibrosis cardíaca, como el ST2 soluble, la galectina-3 o el factor de crecimiento de fibroblastos 23 (FGF-23), así como de los biomarcadores de necrosis miocárdica como la troponina [7, 8].

Se ha estudiado la relación de la proteína de unión a los ácidos grasos cardíaca (HFABP) en multitud de patologías, y esta se ha relacionado con la detección temprana de la isquemia, útil para el diagnóstico temprano del infarto de miocardio [9, 10]. El aumento de HFABP también se ha asociado con la IC, y su determinación podría aportar información suplementaria en la estratificación del riesgo de los pacientes con IC [9, 10].

El objetivo de este estudio es determinar las concentraciones de HFABP en pacientes con IC con fracción de eyección reducida (ICFER) y evaluar su valor pronóstico.

## Materiales y métodos

En nuestro estudio se incluyeron 25 voluntarios sanos sin tratamiento médico y sin antecedentes de hipertensión, diabetes, enfermedad renal crónica o enfermedades cardiovasculares, y 60 pacientes con IC con fracción de eyección ventricular izquierda reducida (ICFER, fracción de eyección (FE) inferior al 35%). El estado funcional de los

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pacientes con IC se determinó según los criterios de la New York Heart Association (NYHA), identificando a 24 pacientes con ICC moderada (NYHA II) y a 36 con ICC grave (NYHA III-IV). En 47 pacientes, la IC fue debida a una miocardiopatía isquémica, presentando el resto miocardiopatía dilatada. Como criterio principal de valoración, se estableció la muerte cardiovascular en un periodo de 3,8 años. Todos los pacientes firmaron el consentimiento informado. El estudio fue aprobado por el comité ético correspondiente.

La HFABP y la troponina fueron determinadas en el analizador Maglumi® 800 (Snibe diagnostics, Shenzhen, China) mediante inmunoensayo de quimioluminiscencia basado en el marcador amino-butil-etil-isoluminol (ABEI). ABEI es una pequeña molécula no enzimática con una fórmula molecular especial, que mejora la estabilidad de las soluciones ácidas y alcalinas.

El proceso de reacción química de ABEI, en el que se emplea hidróxido de sodio ( $\text{NaOH}$ ) y peróxido de hidrógeno ( $\text{H}_2\text{O}_2$ ), finaliza en tres segundos. Se midieron las concentraciones de NT-proBNP en muestras séricas mediante inmunoensayo de quimioluminiscencia en la plataforma Cobas® 8000 (Roche Diagnostics, Mannheim, Germany). El coeficiente de variación interensayo de la troponina I observado en nuestro laboratorio fue del 5,8% para una concentración de 5,3 ng/L. Se validó localmente una concentración de 10 ng/L en el percentil 90 para los sujetos sanos.

Para determinar las concentraciones de galectina-3 (BG Medicine, Waltham, MA, USA) y los fragmentos C-terminales de FGF-23 (Immutopics, San Clemente, CA, USA) se utilizó el ensayo por inmunoadsorción ligado a enzimas (ELISA).

### Análisis estadístico

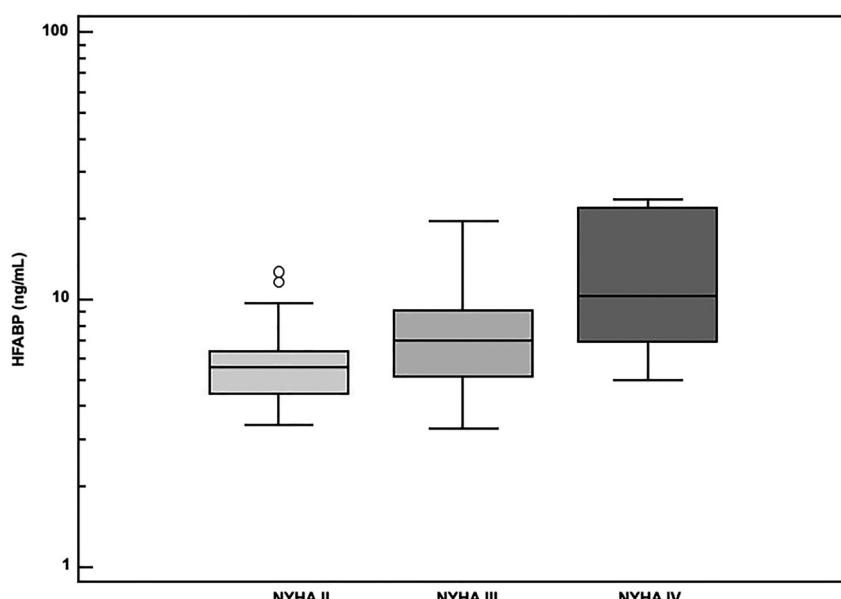
La normalidad en la distribución de las variables se evaluó mediante la prueba de Shapiro-Wilks. Cuando fue necesario, se realizó la transformación logarítmica de los datos, previamente al análisis estadístico. Las diferencias entre los voluntarios sanos y los pacientes con IC se evaluaron mediante análisis de varianza de una vía con la prueba de Student-Newman-Keuls para su comparación por pares. Se calcularon los coeficientes de correlación de Spearman para analizar

las relaciones entre los biomarcadores. La influencia de la edad, la FE y los biomarcadores en la supervivencia se evaluó mediante el análisis univariante de riesgo proporcional de COX. Se estimó la curva de supervivencia de los pacientes con respecto a la mediana de HFABP y se realizó la comparación mediante la prueba de Mantel-Cox. El poder de discriminación entre biomarcadores se calculó mediante el análisis de la curva ROC, con el criterio definido de muerte cardiovascular al final del periodo de seguimiento. Los valores de  $p<0,05$  se consideraron estadísticamente significativos. El análisis estadístico se realizó con el programa informático Medcalc.

## Resultados

El grupo de pacientes con IC estaba compuesto por 15 mujeres y 45 hombres. La media de edad fue de 69,5 años, mientras que la FE media fue de 22,3%. Las concentraciones de HFABP fueron significativamente mayores en los pacientes con IC (mediana: 6,3 ng/mL; rango: 3,3–23,6 ng/mL) frente a los voluntarios sanos (2,2 ng/mL; 0,3–4,5). Se observó una relación significativa entre los niveles de HFABP y las clases funcionales de la NYHA ( $p<0,001$ ), siendo las medias geométricas 5,6 ng/mL en NYHA II, 7,1 ng/mL en NYHA III y 11,1 ng/mL en NYHA IV (Figura 1). Las concentraciones medias de NT-proBNP, troponina I, galectina-3 y FGF-23 fueron de 4517 ng/L, 29,8 ng/L, 18,5 ng/mL y 346 RU/mL, respectivamente. Se observaron correlaciones significativas entre las concentraciones de HFABP, NT-proBNP, la troponina I, la galectina-3 y el FGF-23 (Tabla 1).

Con un seguimiento medio de 3,8 años, 43 pacientes con IC fallecieron (exacerbación de la IC,  $n=28$ ; muerte súbita,  $n=10$ ; otros tipos de muerte CV,  $n=5$ ) y 4 pacientes



**Figura 1:** Niveles circulantes de HFABP en relación con las clases de la New York Heart Association (NYHA).  
HFABP, proteína de unión a los ácidos grasos cardíaca.

**Tabla 1:** Matriz de correlación entre HFABP y marcadores cardíacos en pacientes con IC grave.

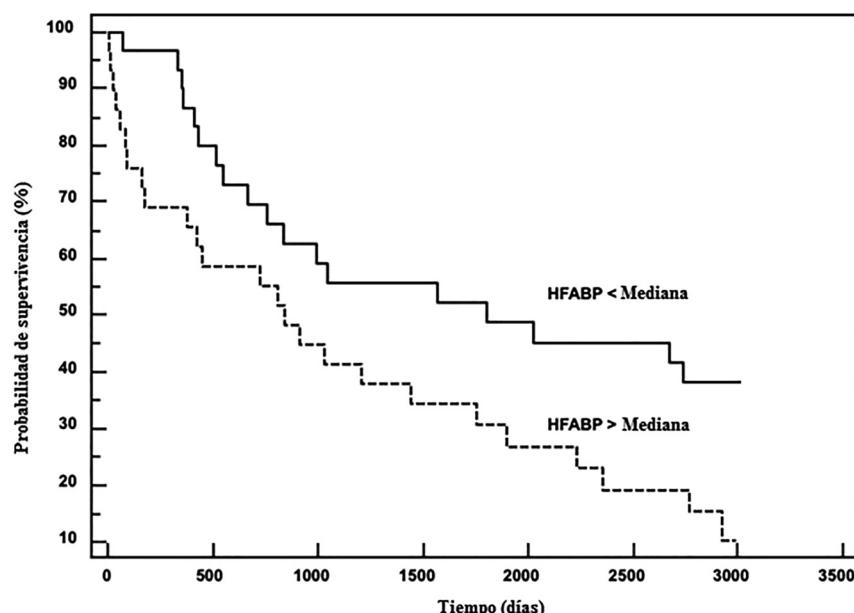
	HFABP, pg/mL	NT-proBNP, pg/mL	Troponina I, ng/mL	Galectina-3, pg/mL	FGF-23, ng/L	
HFABP, pg/mL	—	0,56 <0,001	0,25 0,05	0,68 0,41	0,48 0,67	r valor p
NT-proBNP, pg/mL	0,56 <0,001	—	0,43 <0,001	0,50 0,04	0,67 <0,001	r valor p
Troponina I, ng/mL	0,25 0,05	0,43 <0,001	—	0,14 0,29	0,94 0,009	r valor p
Galectina-3, pg/mL	0,68 0,41	0,50 0,04	0,14 0,29	—	0,56 <0,001	r valor p
FGF-23, ng/L	0,48 <0,001	0,67 <0,001	0,94 0,009	0,56 <0,001	—	r valor p

se sometieron a un trasplante de corazón. La regresión de COX reveló una relación estadísticamente significativa entre los niveles de HFABP y la muerte cardiovascular ( $p=0,016$ ), siendo significativamente divergentes las curvas Kaplan-Meier de los pacientes estratificados según la concentración media de HFABP (prueba de Mantel-Cox:  $p = 0,024$ , Figura 2). El área bajo la curva ROC fue inferior para HFABP, 0,63 (IC95%: 0,53–0,72), comparado con NT-proBNP, 0,74 (0,65–0,82) pero significativamente mayores que para la troponina I, 0,50 (0,37–0,63). Sin embargo, cuando se combinaron NT-proBNP y HFABP en una estrategia multimarcador, la tasa de muerte CV al final del seguimiento fue del 46% en los pacientes con IC y con dos biomarcadores por debajo de la mediana ( $n=18$ ), 69% en los pacientes con IC y con uno de los biomarcadores superior a la mediana ( $n=18$ ); y 88% en los pacientes con IC y con los dos biomarcadores superiores a la mediana

( $n=24$ ). Así, postulamos que, en una estrategia multimarcador, la determinación de HFABP podría aportar un valor añadido de alrededor del 20% con respecto al análisis de NT-proBNP, a la hora de estimar el riesgo en pacientes con IC.

## Discusión

Identificar el subfenotipo de ICFer es importante para desarrollar una estratificación del riesgo personalizada y mejorar el manejo de los pacientes con IC, a lo que puede contribuir el análisis de biomarcadores. Nuestros resultados muestran una correlación positiva entre las concentraciones de HFABP y la gravedad de la IC. La HFABP también está relacionada con biomarcadores conocidos de remodelado cardíaco y con muerte cardiovascular a largo plazo.



**Figura 2:** Curvas de supervivencia Kaplan-Meier en pacientes con IC grave, en función de la concentración de HFABP. IC, insuficiencia cardiaca; HFABP, proteína de unión a los ácidos grasos cardíaca.

Implementar nuevos biomarcadores relacionados con la IC en la clínica sigue resultando complicado, y los posibles candidatos aún tienen que demostrar un buen rendimiento analítico, valor clínico añadido y buena relación coste-efectividad [1, 6]. Nuestros hallazgos demuestran que durante la evolución de la ICFer se libera HFABP, ya que se observó un incremento de los niveles de HFABP según aumentaba la gravedad de la ICFer. También hallamos una intensa correlación positiva de HFABP con la galectina-3 y el FGF-23, dos biomarcadores relacionados con el remodelado cardíaco y, más específicamente, con la inflamación cardiovascular, la fibrosis y la hipertrofia [6, 11]. Los resultados obtenidos concuerdan con estudios recientes, que muestran una correlación estadísticamente significativa entre las concentraciones de HFABP y los parámetros ecocardiográficos de remodelado ventricular izquierdo, y con un mal pronóstico en los pacientes con IC descompensada [12]. Los resultados también muestran que los niveles de HFABP están asociados a un mayor riesgo de muerte cardiovascular, ya que las curvas Kaplan-Meier identificaron un cambio en la supervivencia basado en la mediana de HFABP.

Nuestros resultados coinciden con la literatura actual. De hecho, en estudios previos ya se habían observado niveles elevados de HFABP en la insuficiencia cardíaca con fracción de eyección normal [13]. Existe evidencia de que los pacientes con disfunción ventricular izquierda asintomática muestran niveles de troponina T de alta sensibilidad y HFABP superiores a los voluntarios sanos. En otro estudio reciente, se observó que la medida adicional de HFABP mejoraba la especificidad diagnóstica y el valor predictivo positivo del análisis de NT-proBNP solo [14]. Las concentraciones altas de HFABP se asociaron a un mayor riesgo de muerte a los 5 años, lo cual coincide con nuestras observaciones.

Los datos muestran también que, en la estrategia de múltiples biomarcadores, el análisis de HFABP aportó un valor añadido a la prueba de NT-proBNP para la estratificación del riesgo en pacientes con IC. Estas estrategias que combinan varios biomarcadores son actualmente posibles, gracias a la automatización del HFABP y la determinación simultánea de NT-proBNP, pudiendo contribuir en la identificación de aquellos pacientes con ICFer con mayor riesgo de muerte cardiovascular, lo que podría ayudar a personalizar el manejo de la enfermedad y la selección de tratamiento.

La integración de datos es también prometedora, gracias al uso de la inteligencia artificial y a la oportunidad que ello brinda de combinar los datos clínicos, los biomarcadores y los parámetros ecocardiográficos, lo que podría mejorar la precisión diagnóstica, la estratificación del riesgo y las decisiones clínicas [15].

Cabe señalar que nuestro estudio presenta algunas limitaciones, como el bajo número de pacientes, lo que impide realizar un análisis por rangos intercuartílicos o analizar la relación entre los biomarcadores y la disfunción sistólica y diastólica.

En conclusión, existe una correlación entre las concentraciones de HFABP y la gravedad de la ICFer, habiéndose hallado también una asociación entre la HFABP y marcadores conocidos de la enfermedad, así como con un mayor riesgo cardiovascular. La determinación conjunta de HFABP y NT-proBNP podría ser sinérgica a la hora de identificar el subfenotipo de los pacientes con ICFer, pudiendo contribuir a una atención más personalizada.

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