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## 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 hospitalisations 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/

ml versus  $\approx 0.05$  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  $\leq 3$ -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)	Plasma cut-off (ng/ml)											
	HFABP					HFABP + Tn						
	Population (N)	Tn	HFABP	Time to s/s onset	Sens. (NPV) %	Spec. (PPV)%	AUC	Sens. (NPV)%	Spec. (PPV)%	AUC	Sens. (NPV) %	Spec. (PPV) %
Haastrup, 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
Seino, 2003 [16] (AMI)	NSTEMI = 12.3%	1.0	12		76 (95)	96 (80)		19 (86)	98 (67)		NR	NR
	CP + Non-diagnostic EKG (371)	2.0	15	<2h	62 (93)	97 (81)	0.72	22 (50)	94 (80)	NR	NR	NR
	AMI = 49%	NR (TnT)	6.2	2-4h	89 (80)	52 (69)	0.84	57 (65)	70 (91)		NR	NR
Seino, 2004 [17] (AMI)	CP + I5T or I7Tn (129)	NR (TnT)	6.2	4-6h	100 (100)	40 (57)	0.96	67 (71)	66 (61)	NR	NR	NR
	AMI = 24%	NR (TnT)	6.2	6-12h	95 (90)	55 (55)	NR	94 (95)	68 (62)	NR	NR	NR
		NR (TnT)	6.2	12-24h	100 (100)	63 (44.4)	NR	50 (86.7)	96.3 (80)	NR	NR	NR
Ruzgar, 2006 [18] (ACS)	Patients with ACS (40)	0.01 (TnT)	6.2	<3h	100 (100)	93.8 (75)	NR	0 (78.9)	93.8 (0)	NR	NR	NR
	STEMI = 52%	0.01 (TnT)	6.2	3-6h	75 (93.8)	72.7 (62.5)	NR	60 (84.6)	100 (100)	NR	NR	NR
	NSTEMI = 30%	0.01 (TnT)	6.2	6-12h	100 (100)	75 (62.5)	NR	100 (100)	87.5 (76)	NR	NR	NR
Cavus, 2006 [19] (ACS)	Typical CP < 1 hour (67)	0.1 (TnT)	7	>12h	95.2	100	NR	38.1	100	NR	NR	NR
	STEMI = 27%	0.1 (TnT)	7	<6h	91	100	NR	100	100	NR	NR	NR
	NSTEMI = 10%	0.1 (TnT)	7	6-24h	97.6	88.5	NR	100	23.1	NR	NR	NR
McCann, 2008 [20] (AMI)	Ischaemic CP (415)	0.03 (TnT)	5	4h	97.6	88.5	NR	100	88.5	NR	NR	NR
	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%	NR (TnT)	7	≥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
	AMI = 35%	0.01 (TnI)	2	<3h	100	75	0.967 (<6h)	100	20	0.556	NR	NR
	Sudden CP + dyspnea/syncope/nausea / vomiting <6h duration (83)	0.01 (TnI)	2	3-6h	97	68	NR	75	21	(<6h)	NR	NR
Halterm, 2010 [23] (AMI)	STEMI = 58%	0.03 (TnT)	7.3	<6h (all)	98	71	NR	77	20	NR	NR	NR
	NSTEMI = 6%	0.03 (TnT)	7.3	<4h	86 (92)	66 (50)	0.76 (<4h)	42 (81)	100 (100)	0.71 (<4h)	93 (96)	66 (52)
	Ischaemic-type CP (94)	0.03 (TnT)	7.3	>4h	59 (72)	64 (50)	0.71 (all)	100 (100)	100 (100)	0.87(all)	100 (100)	64 (63)
Kim, 2010 [24] (AMI)	STEMI = 12%	0.1 (TnT)	19	<2h	60	77.4 (all)	0.78 (all)	20.2	98.1 (all)	0.82 (all)	33.3	NR
	NSTEMI = 16%	0.1 (TnT)	19	2-4h	64.7			17.7			82.4	NR
	CP suggesting AMI (117)	0.1 (TnT)	19	4-6h	91.7			58.3			91.7	NR
McMahon, 2012 [25] (AMI)	AMI-55%	0.37 (TnI)	5.24	6-12h	88.9			66.7			80	NR
	CP considered cardiac (1128)	0.37 (TnI)	5.24	<3h	64.3 (93)	84.2 (43)	0.84	50 (92)	93.3 (60)	0.76	71.4 (94)	NR
	AMI = 10%	0.37 (TnI)	5.24	3-6h	85.3 (97)	88.7 (55)	0.89	67.6 (95)	94.3 (66)	0.85	88.2 (98)	NR
Garcia-Valdecasas, 2011 [26] (AMI)	Ischaemic CP within 6h (165)	0.6 (TnI)	6.2	6-12h	89.9 (98)	93.5 (70)	0.94	81 (97)	94.2 (70)	0.90	92.4 (99)	NR
	AMI = 40%	0.6 (TnI)	6.2	12-24h	90.1 (99)	91.4 (56)	0.97	95.8 (99)	94.3 (71)	0.98	NR (100)	NR
	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)	AMI = 15.6%	0.028 (TnI)	60	<6h	81 (80)	50 (52)	0.72	25 (65)	91 (64)	0.66	NR	NR
	NSTEMI = 15.6%	0.028 (TnI)	60	≤4h	50 (90.7)	89.8 (47.6)	NR	85 (95.1)	94.7 (81)	NR	86.7 (97.2)	87 (55.3)
	Ischaemic-type CP > 30 min duration (48)	0.04 (TnI)	7	<3h	89 (86)	100 (100)	NR	33 (50)	100 (100)	NR	NR	NR
Vupputuri, 2015 [29] (AMI)	NSTEMI = 50%	0.14 (TnI)	6.4	3-6h	70 (73)	89(88)	NR	70 (67)	67 (70)	NR	NR	NR
	CP suggestive of ischaemia (77)	0.14 (TnI)	6.4	>6h	100 (100)	89 (83)	NR	100 (100)	89 (83)	NR	NR	NR
	AMI > 50%	0.14 (TnI)	6.4	≤6h	100 (100)	85.7 (85.2)	NR	46.1 (63.6)	100 (100)	NR	NR	NR

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.

AMI: Acute myocardial infarction; ACS: acute coronary syndrome; CP: Chest pain; NSTEMI: non ST-elevation myocardial infarction; 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 ( $R^2=0.36$ ).

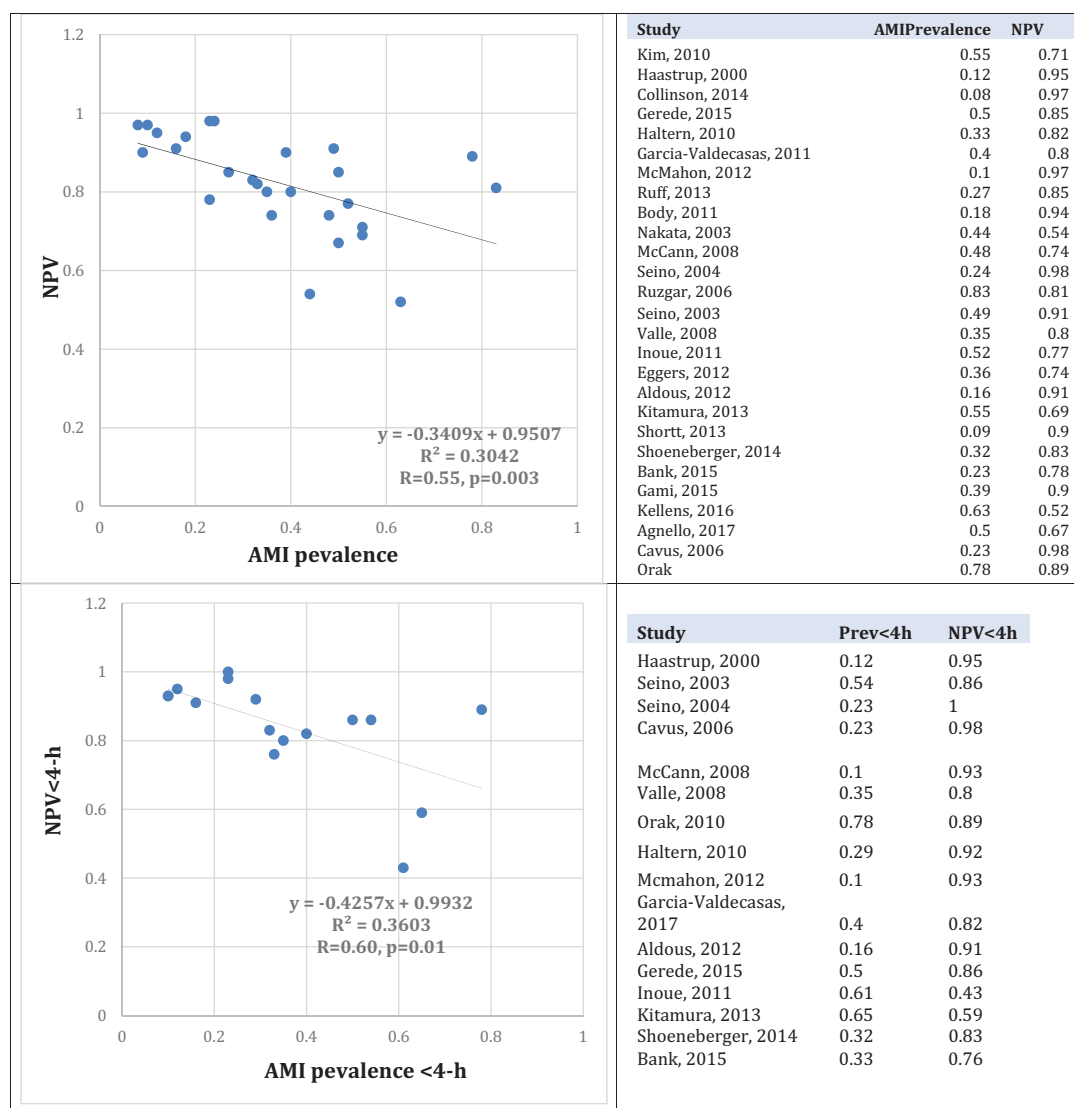
It should be noted that since most reports did not report AMI prevalence in each time from symptom onset sub-group, we assumed that AMI prevalence in each sub-group was not significantly different from the overall prevalence. Though a possible source of error, we believe that the prevalence of AMI among 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].

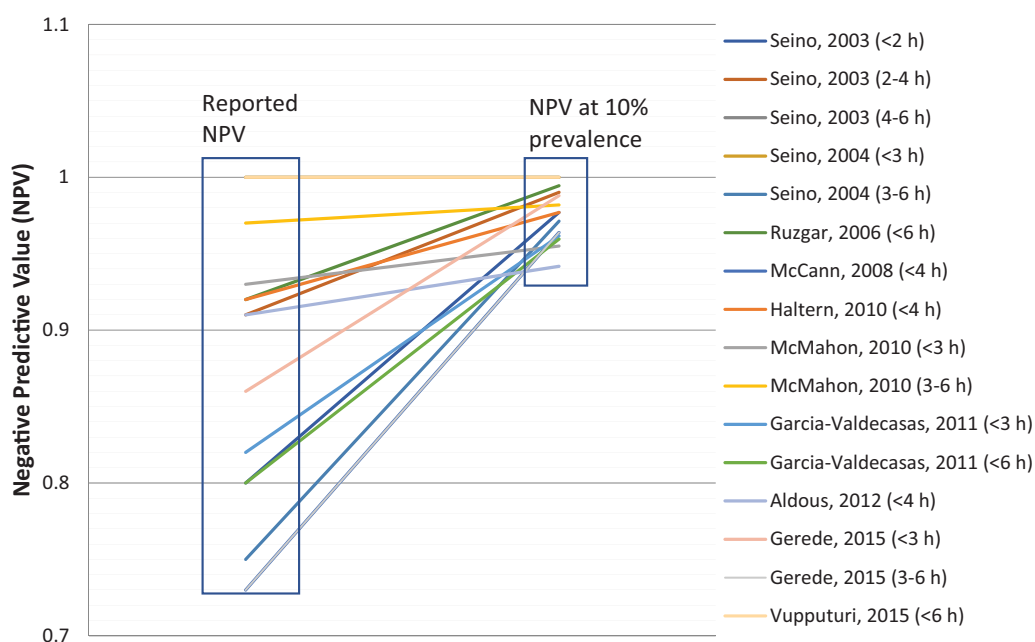
Finally, given the staggered time course of the two markers’ rise in plasma, combining them may aid in better assessing the onset time of ischaemia. Hence, patients with an uncertain time of symptom-onset, a positive H-FABP with a normal cTn will likely mean duration of symptoms of 0–4 h, whereas a normal 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  $\approx 6$  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-FABP 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 miniscule 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)	HFABP	Time to s/s	HFABP				hs-Tn				hs-Tn + H-FABP			
					Sens. (NPV)	Spec. (PPV)	AUC	Sens. (NPV)	Spec. (PPV)	AUC	Sens. (NPV)	Spec. (PPV)	Sens. (NPV)	Spec. (PPV)		
Inoue, 2011 [30] (ACS)	CP > 20 min (432) STEMI = 52% NSTEMI = 9%	0.014 (hs-TnT)	6.2	<2 h	79 (42)	66 (87)	0.70	72 (40)	57 (84)	0.68	72 (40)	57 (84)	79.7 (86.9)	74.6 (63.4)	NR	NR
Eggers, 2012 [31] (AMI)	CP + no STEMI (360) NSTEMI = 35.6%	0.014 (hs-TnT)	5.8	<4 h	28.6	73 (41)	0.69	77 (38)	48 (83)	0.67	77 (38)	48 (83)	79.7 (86.9)	74.6 (63.4)	NR	NR
Aldous, [2012 [27] (AMI)	CP s/o AMI, no STEMI (384) NSTEMI = 15.6%	0.014 (hs-TnT)	6	<4 h	39.1 (73.8)	76 (43)	0.74	83 (44)	52 (86)	0.72	83 (44)	52 (86)	90 (97.5)	73.5 (38.6)	NR	NR
Kitamura, 2013 [32] (AMI)	S/S suggestive of AMI (85) NSTEMI = 12%	0.014 (hs-TnT)	6.2	<2 h	38 (57)	93 (86)	0.70	25 (40)	57 (40)	0.48	25 (40)	57 (40)	NR	NR	NR	NR
Shorrt, 2013 [33] (AMI)	STEMI = 43% Possible ACS s/s < 6 h (163) AMI = 8.6%	0.014 (hs-TnT)	5.2	<6 h	43 (90)	100 (100)	0.81	100 (100)	81 (67)	0.96	100 (100)	81 (67)	86 (96)	54 (21)	NR	NR
Shoenberger, 2014 [34] (AMI)	CP s/o AMI (105) AMI = 32.4%	0.014 (hs-TnT)	5.76	<1 h	58.8 (83.3)	98.6 (95.2)	0.84	70.6 (85.9)	85.9 (70.6)	0.88	70.6 (85.9)	85.9 (70.6)	NR	NR	NR	NR
Bank, 2015 [35] (ACS)	CP s/o ACS, no STEMI (453) NSTEMI = 23%	0.014 (hs-TnT)	7	<3 h	47 (76)	85 (61)	0.73	63 (83)	92 (81)	0.86	63 (83)	92 (81)	69 (84)	83 (68)	NR	NR
Gami, 2015 [36] (AMI)	CP < 6 h (88) AMI = 38.6%	0.014 (hs-TnT)	5	>6 h	68 (89)	79 (50)	0.78	64 (89)	89 (64)	0.86	64 (89)	89 (64)	71 (86)	79 (59)	NR	NR
Kellens, 2016 [37] (AMI)	Typical CP (152) STEMI = 33% NSTEMI = 30%	(hs-TnT)	5.3	158 min (median)	54 (52)	88 (82)	0.89	94 (94)	62 (61)	0.8	94 (94)	62 (61)	100 (100)	88.9 (85)	NR	NR
Agnello, 2017 [38]	CP < 1-h duration + normal cTn (n = 28 CP + 28 controls)	(hs-TnT)	6.1	<1 hour	55.5 (67)	89.2 (83)	0.65	34 (60.4)	100 (100)	0.80	34 (60.4)	100 (100)	NR	NR	NR	NR

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	HFABP 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	Amission 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 cTnI (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	HR 2.6, 1.1–6.5 per 3.86ng/ml increase
				cTn	HR 7, 1.1–44
				BNP	NS
				ANP	NS
Arimoto, 2005 [85]	Acute CHF (179)	Cardiac death CHF readmission	20-mo	H-FABP	HR 7.39, p=0.0065
				LDH	NS
				CK	NS
				H-FABP	HR 5.42, 2.20–13.32
Niizaki, 2005 [86]	Acute CHF (186)	Cardiac death CHF readmission	534 ± 350 days	BNP	HR 2.41, 1.02–5.73
				H-FABP	RR 7.5, 0.7–36.1
Komamura, 2006 [87]	Chronic stable non-ischaemic DCM (92)	Cardiac death Heart transplant LV assist device	48 months	BNP	RR 10.9, 3.5–35.3
				H-FABP	NS
Niizeki, 2007 [88]	Acute CHF (126)	Cardiac death CHF readmission	474 ± 328-days	H-FABP	HR 15.7, 3.8–64.5
				BNP	HR 2.6, 0.87–7.8
Niizek, 2008 [89]	Acute CHF (113) (Admission + discharge)	Cardiac death CHF readmission	624 ± 299 days	H-FABP (at discharge)	HR 5.7, 2–9.5
				BNP (at discharge)	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	HR 2.24, 1.21–4.14
				cTn	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	HR 1.165, 1.034–1.314
				cTn	NS
				BNP	NS
				hs-CRP	NS
Hoffmann, 2015 [82]	Acute CHF (122)	All-cause death CHF readmission	5-yrs	H-FABP	ACM-NS CHF readmit-HR 1.07, 1.02-1.13
				cTn	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	HR 1.57, 1.2–2
				cTn-AF	HR 1.28, 1.04–1.58
				cTn-SR	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	BNP-AF/SR	NS
				H-FABP	HR 5.1, 1.86–14.17
				hs-Tn	NS
				BNP	NS
Kadowaki, 2017 [94]	Acute CHF (322)	Cardiac death CHF readmission	534 (203-1014) days	H-FABP	HR 1.745, 1.088–2.7903
				BNP	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)	(OR 1.3, 1.06–1.68)
				BNP	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-pro-BNP (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 sub-par 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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