Is there a place for heart-type fatty acid binding protein in the era of high-sensitive cardiac troponin T for the diagnosis of acute myocardial infarction? A systematic review

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Abstract

Early recognition of myocardial infarction (MI) remains a challenge, especially in patients presenting with non-ST-segment elevation MI. Heart-type fatty acid binding protein (hFABP) has shown to be a more sensitive marker for myocardial necrosis as compared to non-high sensitive troponins (4th generation and older). However, since high sensitive troponin (hs TnT) assays are available, it is questionable whether hFABP still has value as a diagnostic tool for MI. A systematic search was conducted in Medline, Embase and Cochrane. After selecting the articles, they were assessed for risk of bias according to the QUADAS-2 criteria. Negative predictive value, positive predictive value, sensitivity and specificity were extracted or calculated if possible. Nine studies met the inclusion criteria. Overall, hs TnT showed higher sensitivity than hFABP, while hFABP had higher specificity. In patients presenting within 3 hours after onset of symptoms, sensitivity is low for both hFABP and hs TnT (19-63% *vs* 25-55%, respectively), while specificity seems higher for hFABP than for hs TnT (70-99% *vs* 57-86%, respectively). In these patients, the area under the curve for hs TnT is equal or better than that for hFABP (0.67-0.92 for hs TnT *vs* 0.69-0.85 for hFABP). The addition of hFABP to hs TnT did not improve sensitivity and specificity. This systematic review finds no advantage for using hFABP over hs TnT in either early presenting patients or overall. Furthermore, no advantage was found if a combination of hFABP and hs TnT was used for the diagnosis of MI.

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Introduction

It is important to diagnose myocardial infarction (MI) as soon as possible, to improve the prognosis by timely intervention and reduce the time in the emergency department. However, early diagnosis of MI remains a challenge, especially in patients with non-ST-segment elevation MI (NSTEMI) or in patients presenting early after onset of symptoms.

According to the European Society of Cardiology guidelines, MI is diagnosed by an increase of a cardiac biomarker, with at least one value above the 99th percentile of the upper reference limit, in combination with signs of ischemia. These can either be clinical symptoms, ECG changes or abnormalities seen on imaging.[1] High sensitive cardiac troponin is the preferable cardiac biomarker to diagnose MI, because it has a higher sensitivity and specificity than other laboratory tests, like creatine kinase (CK), and its MB isoenzyme (CK-MB).[2] Although diagnostic sensitivity in the first hours after symptom onset has improved since the introduction of high sensitive assays, guidelines still recommend to redo the test after 1 or 3 hours if a negative result is found for patients presenting within 6 hours after onset of symptoms.[1] However, most patients present within 2-3 hours of symptom onset.[3]

Heart-type fatty acid binding protein (hFABP) has been proposed as an addition to or replacement for CK-MB and cardiac troponin, because of a higher sensitivity for myocardial damage in patients presenting early after symptom onset compared to non-high sensitive troponins.[4] Many of the previously published reviews did not look specifically at hFABP in comparison to high-sensitive troponins. The aim of this systematic review is to assess whether hFABP can be a replacement or addition to high-sensitive troponin T (hs TnT) for the diagnosis of MI in general practice, and more specifically in patients presenting within 3 hours after symptom onset. Both hs TnT and high sensitive troponin I assays are available. Due to the heterogeneity between the different troponin I assays, we have chosen to compare hFABP to hs TnT only.

Methods of research

Search strategy

A systematic literature search was conducted using Medline, Embase and Cochrane databases of all literature until the 19th of March 2018. The search was constructed by combining *high sensitive troponin t* and *heart type fatty acid binding protein* and *myocardial infarction* (see the Appendix for full search). After removing duplicates, all publications were independently screened by the first two authors on title and abstract, using predetermined in- and exclusion criteria. The inclusion criteria were: diagnostic cohort study; inclusion of patients ≥18 years suspected of an acute coronary syndrome (ACS); testing of both hFABP and hs TnT prior to the diagnosis; cut-off value for hs TnT>14ng/L; and NSTEMI or a combined outcome of NSTEMI and STEMI as outcome variable. We excluded studies in which ACS, including unstable angina pectoris, was used as the primary outcome variable, studies which were not available in English or Dutch, were performed in the primary care setting, were non-human studies or if no full text version was available. We did not discriminate between studies using lab tests or point-of-care tests for determining hFABP or hs TnT.

The remaining publications were screened for full text. The references of the included publications were screened in Web of Science and Scopus to check for additional relevant publications. Any disagreement was resolved by discussion between the first three authors.

Assessment for risk of bias

All included publications were independently screened by the first three authors (DMFC, DOC, TOB) for the risk of bias, based on predefined criteria. These criteria are a modified version of the QUADAS-2 criteria for diagnostic research.[5] We assessed whether there was more than 10% missing data, if there was standardization for how both the determinant and the outcome parameter were determined, if the blood samples for hFABP and hs TnT were collected at the same time, if there was a pre-specified cut-off value for hFABP and if the outcome assessor was blinded for the results of the hFABP test. Furthermore, we assessed whether there was a risk of bias in the inclusion process. Exclusion of STEMI patients was allowed, since it is not standard practice to test for cardiac troponin in these patients. Any disagreement was resolved by discussion between the first two authors and the third author. For each item, one point was awarded if specific criteria were met. Studies scoring six or seven points were assessed as having a low risk of bias, studies scoring four or five points were assessed as having a medium risk of bias and studies scoring less than four points were assessed as having a high risk of bias.

Data extraction and analysis

Data regarding prior probability, positive and negative predictive value (PPV and NPV), sensitivity and specificity and their 95% confidence intervals were extracted from the full text article. If these parameters were not presented, they were calculated using the available data using the statistical program 'R' (CRAN project) or the area under the curve (AUC) was extracted from the article if this was available. We choose not to perform a meta-analysis, due to differences in cut-off values and outcome parameters in the selected studies. We also analysed the combination of hFABP and hs TnT and compared hFABP with hs TnT in patients presenting within 3 hours after onset of symptoms.

Results

Search strategy

Our search yielded 232 unique publications, which were subsequently screened on inclusion and exclusion criteria, using the title and abstract. Of these, 35 publications were screened on full text and finally 9 publications were adjudicated for risk of bias (Figure 1). An overview of the included publications is presented in Table 1.[6-14]

Risk of bias assessment

Table 2 shows the risk of bias assessment.[6-14] All publications were either prospective or retrospective cohort studies. One of the studies was adjudicated as having a high risk of bias, one of the studies was adjudicated as having a medium risk of bias and all other studies as having a low risk of bias.

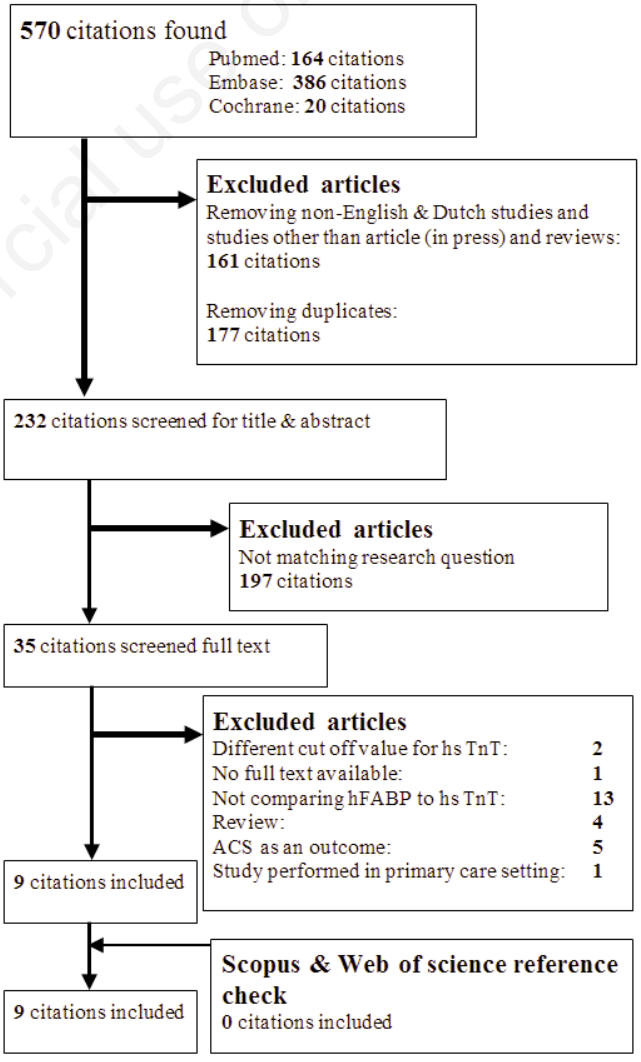

Figure 1. Literature search results. Hs TnT, high-sensitive troponin T; hFABP, heart-type fatty acid binding protein; ACS, acute coronary syndrome.

Data analysis

Results of the studies are shown in Table 3.[6-12,14] The last column specifies whether NSTEMI or MI was used as the outcome parameter. In two of the studies the NPV was significantly higher for hs TnT as compared to hFABP, while there were no significant differences in the PPV. Specificity of hFABP was significantly better in two studies, while the sensitivity of hs TnT was significantly better in one study. Overall, NPV and sensitivity seemed to be higher for hs TnT, while PPV and specifity seemed to be higher for hFABP.

Table 4 shows the results from the different studies on early presenters.[9,11-13] Only the study from Schoenenberger *et al*. focused specifically on early presenting patients.[13] Studies reporting an AUC have equal results or showed an advantage for hs TnT over hFABP. Studies reporting a PPV showed an advantage for hFABP. However, no statistical significance was either found or reported in these studies. No difference in NPV was found.

Table 1. Overview of included studies.

Authors	Year of publication	Study design	Number of patients (N)	Male (%)	Age	Time from symptom onset to presentation (hours)	hFABP cut-off value (µg/L)	Outcome parameter	Prevalence of outcome (%)
Cappellini *et al.*[6]	2013	Retrospective cohort	67	67	74 (mean)	NA	3.49	NSTEMI	33
Eggers *et al.*[7]	2012	Retrospective cohort	360	66	67 (mean)	<8	5.8	NSTEMI	36
Gami *et al.*[8]	2015	Prospective cohort	88	NA	NA	<6	5.09	MI	39
Inoue *et al.*9	2011	Retrospective cohort	432	73	67 (median)	<24	6.2	NSTEMI	9
Kellens *et al.**[10]	2016	Prospective cohort	203	81	63 (NA)	<24	5.3	MI	63
Kitamura *et al.*[11]	2013	Prospective cohort	85	78	67 (median)	<24	6.2	MI	55
Reiter *et al.*[12]	2013	Prospective cohort	1037	67	64 (median)	<12	4.2	NSTEMI	16
Schoenenberger *et al.*[13]	2016	Prospective cohort	105	70	61 (mean)	<1	4.0	NSTEMI	32
Willemsen *et al.*[14]	2015	Prospective cohort	202	78	62 (median)	<24	4.0	MI	17

hFABP, heart-type fatty acid binding protein; NA, not available; NSTEMI, non-ST-elevated myocardial infarction; MI, myocardial infarction. *Point-of-care test used for heart-type fatty acid binding protein.

Table 2. Risk of bias analysis.

Authors	Missing data	Patient selection	Standardization of determinant	Pre-specified cut-off value	Blood sample collection	Outcome standardization	Blinding for hFABP	Risk of bias
Cappellini *et al.*[6]	+	-	+	+	+	+	+	Low
Eggers *et al.*[7]	-	+	+	+	+	+	+	Low
Gami *et al.*[8]	NA	-	+	-	+	+	NA	High
Inoue *et al.*9	NA	-	+	+	+	+	+	Medium
Kellens *et al.**[10]	+	+	+	+	+	+	NA	Low
Kitamura *et al.*[11]	+	-	+	+	+	+	+	Low
Reiter *et al.*[12]	+	-	+	+	+	+	+	Low
Schoenenberger *et al.*[13]	+	-	+	+	+	+	+	Low
Willemsen *et al.*[14]	+	+	+	-	+	+	+	Low

Legend	
Missing data	+ ≤10% missing data - >10% missing data
Patient selection	+ No exclusion or only STEMI patients excluded - Other patients excluded
Standardization of determinant	+ Standardized protocol to test for hs TnT and hFABP - No standardized protocol to test for hs TnT and hFABP
Pre-specified cut-off value	+ pre-specified cut-off value for hFABP - no pre-specified cut-off value for hFABP
Blood sample collection	+ Blood sample collected at the same time - Blood sample not collected at the same time
Outcome standardization	+ Standardized method to determine outcome - No standardized method to determine outcome
Blinding for hFABP	+ Outcome assessor blinded for hFABP result - Outcome assessor not blinded for hFABP result

Low risk of bias: 6 or 7 +, medium risk of bias 4 or 5 +, high risk of bias <4 +. hFABP, heart-type fatty acid binding protein; hs TnT, high-sensitive troponin T; NA, not available; STEMI, ST-elevated myocardial infarction. *Point-of-care test used for heart-type fatty acid binding protein.

Table 5 shows the results when hs TnT and hFABP were combined to diagnose MI.[7,8,10,12,13] Compared to hs TnT alone, the studies from Eggers *et al*. and Schoenenberger *et al*. found no significant differences, whilst the study from Reiter *et al*. found a better AUC for hs TnT alone. Gami *et al*. found a higher PPV and specificity whilst Kellens *et al*. found a slightly higher sensitivity and NPV.[8,10]

Discussion and Conclusions

The aim of this systematic review was to study the value of hFABP as a marker for myocardial necrosis, alone or added to hs TnT. hFABP is known to rise very early after myocardial necrosis occurs (as soon as 30 minutes after onset of symptoms) and peaks in the blood after approximately 6-8 hours.[15] hFABP was reported to be more specific to myocardial tissue compared to other biomarkers, like myoglobin and CK-MB.[16] Compared to non-high sensitive cardiac troponins, hFABP has shown promising results for the diagnosis of MI, especially early after symptom onset.[4] Multiple studies report higher sensitivity for the combination of troponin and hFABP compared to troponin alone.[17-19] However, these studies and most published reviews have compared hFABP with non-high sensitive troponins instead of the (more accurate and now widely used) hs TnT.[20]

Though many of the studies in this review used a combined outcome of both NTEMI and STEMI, the latter group is not routinely tested, since the ST-segment elevation on the ECG usually is enough to confirm the diagnosis of MI. In patients without these clear ECG changes, the ideal test for myocardial damage combines

Table 3. Heart-type fatty acid binding protein vs high-sensitive troponin T in patients suspected of myocardial infarction.

Authors	NPV (%) (95%CI)		PPV(%) (95%CI)		Specificity (%) (95%CI)		Sensitivity (%) (95%CI)		Outcome parameter
	hFABP	hs TnT	hFABP	hs TnT	hFABP	hs TnT	hFABP	hs TnT	
Cappellini *et al.*[6]	100 (76-100)	88 (69-97)	44 (30-60)	49 (32-66)	39 (25-55)	56 (40-71)	100 (80-100)	85 (61-96)	NSTEMI
Eggers *et al.*[7]	74 (69-79)	87[a] (81-90)	81 (69-90)	63 (55-71)	95 (91-97)	75 (69-80)	39 (31-48)	79[a] (71-86)	NSTEMI
Gami *et al.*[8]	90 (79-97)	94 (81-99)	82 (66-93)	61 (47-75)	88[a] (77-96)	62 (49-76)	85 (69-95)	94 (80-99)	MI
Inoue *et al.*[9]	77	86	60	54	78	61	59	83	NSTEMI
Kellens *et al.**[10]	52	61	85	82	84	73	54	72	MI
Kitamura *et al.*[11]	69 (52-81)	69 (52-83)	91 (76-98)	76 (61-87)	92 (79-98)	71 (54-85)	66 (51-79)	74 (60-86)	MI
Reiter *et al.*[12]	94 (92-95)	98[a] (97-99)	41 (35-47)	42 (37-47)	80 (77-82)	77 (74-80)	72 (65-89)	93 (88-96)	NSTEMI
Willemsen *et al.*[14]	94	93	36	34	71	71	78	73	MI

NPV, negative predictive value; CI, confidence interval; PPV, positive predictive value; hFABP, heart-type fatty acid binding protein; hs TnT, high-sensitive troponin T; NSTEMI, non-ST elevated myocardial infarction; MI, myocardial infarction. *Point-of-care test used for heart-type fatty acid binding protein. [a]Significant difference between hFABP and hs TnT.

Table 4. Heart-type fatty acid binding protein vs high-sensitive troponin T in early presenters (<3 hours since symptom onset).

Authors	Time to presentation (hours)	NPV (%) (95%CI)		PPV (%) (95%CI)		Specificity (%) (95%CI)		Sensitivity (%) (95%CI)		AUC (95%CI)	
		hFABP	hs TnT	hFABP	hs TnT	hFABP	hs TnT	hFABP	hs TnT	hFABP	hs TnT
Inoue *et al.*[9]	3	NA	NA	NA	NA	NA	NA	NA	NA	0.69 (0.58-0.81)	0.67 (0.56-0.78)
Kitamura *et al.*[11]	2	57 (34-77)	40 (19-64)	86 (42-100)	40 (12-74)	93 (66-100)	57 (29-82)	38 (15-65)	25 (7-52)	NA	NA
Reiter *et al.*[12]	3	NA	NA	NA	NA	NA	NA	NA	NA	0.85 (0.82-88)	0.92[a] (0.89-0.94)
Schoenenberger *et al.*[13]	1 AUC: 2	90	91	89	50	99	86	50	63	0.81 (0.75-0.87)	0.90 (0.86-0.94)

NPV, negative predictive value; CI, confidence interval; PPV, positive predictive value; AUC, area under the curve; hFABP, heart-type fatty acid binding protein; hs TnT, high-sensitive troponin T. [a]Significant difference between hFABP and hs TnT.

Table 5. Combination of heart-type fatty acid binding protein and high-sensitive troponin T for the diagnosis of myocardial infarction.

Authors	NPV (%) (95%CI)	PPV (%) (95%CI)	Specificity (%) (95%CI)	Sensitivity (%) (95%CI)	AUC (95%CI)	
					hs TnT	hs TnT and hFABP
Eggers *et al.*[7]	87 (82-91)	63 (55-70)	75 (69-80)	80 (72-86)	NA	NA
Gami *et al.*[8]	100	85	89	100	NA	NA
Kellens *et al.**[10]	70	83	71	82	NA	NA
Reiter *et al.*[12]	NA	NA	NA	NA	0.94[a] (0.92-0.95)	0.88 (0.86-0.90)
Schoenenberger *et al.*[13]	NA	NA	NA	NA	0.85 (0.76-0.95)	0.92 (0.84-0.99)

NPV, negative predictive value; CI, confidence interval; PPV, positive predictive value; AUC, area under the curve; hs TnT, high-sensitive troponin T; hFABP, heart-type fatty acid binding protein. *Point-of-care test used for heart-type fatty acid binding protein. [a]Significant difference.

high sensitivity with high specificity to quickly discriminate between patients who can be send home safely and patients that should be admitted and treated for MI. Our review shows that the sensitivity of hs TnT was found to be higher in six of the eight studies.[7-12] However, only in two of studies the difference was significant. In the studies from Cappellini *et al*. and Willemsen *et al*., sensitivity of hFABP was found to be higher than that of hs TnT (100% *vs* 85% and 78% *vs* 73% respectively).[6,14] This higher sensitivity can be explained by the low cut-off value that was used (3.49µg/L and 4.0µg/L respectively). Earlier studies have shown that the median of hFABP for patients without MI was 3.9µg/L (1.7-7.9 (interquartile range)).[4] Consequently, this high sensitivity comes with a low specificity, especially in the study from Cappellini *et al.*, of only 39%.[6] This is contrary to the other studies, in which a higher specificity for hFABP is found.[7-12] Since the risk of death is almost twofold when the diagnosis of MI is missed, high sensitivity is thought to be of more importance than specificity in this patient group.[21]

In patients presenting early after symptom onset, the results of the two biomarkers are comparable. Although hFABP seems to be a valuable tool for early diagnosis, its sensitivity, even in the early hours, is not better than that of hs TnT. It must be noted that there is a wide variation in both sensitivity and specificity between different studies. However, with a sensitivity of just 50-60%, hFABP cannot replace hs TnT assays as a standalone test for the diagnosis of a MI. This finding is in line with a systematic review by Bruins Slot *et al*. in 2010, comparing hFABP with other biomarkers like CK, CK-MB and non-high sensitive troponins, although in this review almost half of the included studies used POC tests and/or different definitions for MI.[22]

The three studies that reported sensitivity and specificity for the combination of high sensitive troponin T assays and hFABP all show similar or increased specificity for the combined tests.[7,8,10] This is in contrast with our expectations, since in different reviews sensitivity increases when combined tests are performed, at the cost of a loss in specificity.[17,23] For example, in a recently published article by Young *et al*., looking specifically at combining ECG with hs TnT and hFABP for the diagnosis of acute MI, sensitivity increased from 94.8% (ECG or hs TnT) to 97.2% (ECG or hs TnT or hFABP), while specificity decreased from 69.6% to 43.6%.[24] The studies in our review provided no clear explanation for this discrepancy.

The comparison of hFABP to hs TnT is hampered by a major methodological problem, because hs TnT are used as the gold standard for the diagnosis of MI.[1] Most of the studies we included for our review tried to solve this problem by using multiple independent physicians and all medical data available (including ECGs, lab results and coronary angiograms) to confirm the diagnosis of MI. However, it will be very difficult for any cardiac biomarker to outperform hs TnT. With this limitation in mind, we found no convincing evidence that hFABP, alone or in combination with hs TnT, has a better diagnostic performance compared to hs TnT, if hs TnT is easily available.

An important advantage for hFABP is the availability as point-of-care (POC) test, which can be used when classic laboratory tests like hs TnT are not available, for instance in the pre-hospital setting.[10,14,25-27] However, in a review by Bruins Slot *et al*. published in 2013, NPV was too low to safely exclude MI diagnosis when using the hFABP POC test, although many studies were of poor quality.[25] Also, a recently published study by Bank *et al*. found that the used POC test was inferior to the hs TnT test.[26] However, newer POC tests have been introduced since, for instance from FABPulous BV (Maastricht, the Netherlands), which was used in the studies by Kellens *et al*. included in our review. Furthermore, POC TnT tests are being developed and first results of the newer generation tests have recently been published.[28,29] Even though the limit of detection in the newer generation POC tests is less than half of that of the older generation, it is still more than tenfold higher than that of the high sensitive troponins (40ng/L and 3ng/L, respectively).[29] Further research is necessary to study the value of POC tests in the pre-hospital setting.

Concluding, no convincing evidence was found to support the use of hFABP instead of, or in combination with hs TnT for the diagnosis of myocardial infarction, neither in early presenting patients nor in patients presenting after more than 3 hours after onset of symptoms.

Limitations

There are a few limitations to this review to mention. First, different cut-off levels were used for hFABP, which has major influence on NPV, PPV, specificity and sensitivity, leading to difficulty in comparing the different studies. Second, there was a large variation in the prevalence of NSTEMI and MI between the different studies (9-63%). A higher prevalence leads to a higher PPV and a lower NPV and a different population does not only effect the prevalence, but it can also affect the sensitivity and specificity of a diagnostic test.[30,31] This variation can therefore have a major influence on the results. Last, only one study specifically investigated patients presenting early after onset of symptoms. In all other studies this was only a sub-group analysis.

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