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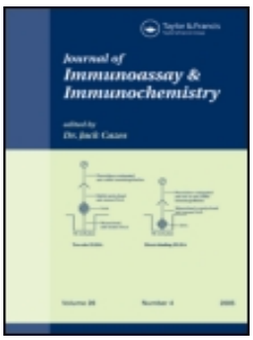

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CARDIODETECT RAPID TEST FOR THE DIAGNOSIS OF EARLY ACUTE MYOCARDIAL INFARCTION

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□ *Two hundreds patients suspected of acute myocardial infarction presenting to the hospital with a median symptom onset of 2.3 h (IQR 1.7–4.0 h) were enrolled in this study. The diagnostic performances of CardioDetect®, a one-step immunotest for heart-type fatty acid-binding protein (H-FABP), and its combination with cardiac troponin I (cTnI) at admission and 2 h after admission, were compared with different cardiac markers. The H-FABP immunotest had better sensitivities (76.6% and 94.4%) than the other cardiac markers and better specificities (88.2% and 81.7%) than myoglobin at admission and 2 h after admission. Both sensitivity and negative predictive value increased to over 90.0% at 2 h after admission. The areas under the receiver operator characteristic curve for the combination of H-FABP with cTnI were the greatest at admission [0.834 (95% CI: 0.774–0.894)].*

Keywords acute myocardial infarction, cardiac marker, cardiac troponin I, diagnosis, heart-type fatty acid-binding protein, myoglobin

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INTRODUCTION

Cardiovascular disease has been increasing in the past few decades in China, the largest and most populous developing country in the world. Coronary artery disease used to be rare in China; however, this is no longer true in modern China. In 2007, there were 22,120 visits for cardiovascular diseases to the Emergency Department (ED) of FuWai Hospital—the biggest Cardiovascular Institute in China; however, out of the total visits, 9,128 of them suffered from chest pain and only 975 of these patients are ultimately diagnosed as acute myocardial infarction (AMI) compared with 3,303 diagnosed as angina pectoris. From the ED perspective, it is important to expeditiously distinguish between AMI and non-AMI patients. Although electrocardiogram (ECG) is a standard test to identify patients with AMI upon ED presentation, it still has relatively low sensitivity for detection of AMI (only 35–50%).[1]

Cardiac markers are the next most commonly used test to identify patients suspected of AMI. Current cardiac markers for evaluation of suspected myocardial infarction include creatine kinase MB fraction (CK-MB), myoglobin (Myo), and troponins. Recommended uses for each marker vary according to their cardiac specificity, sensitivity, release kinetics, ease of measurement, turnaround time for test results, and diagnostic and prognostic uses.

Heart-type fatty acid binding protein (H-FABP) has been suggested as an early cardiac marker for diagnosis of AMI.[2–4] It is a small cytosolic protein that is abundant in cardiac tissue. It is responsible for the intracellular transport of the insoluble fatty acids within the cells. Its concentration in the plasma of healthy persons is relatively low at 0.3–6.0 μg/L.[5,6] Myocardial ischemia results in a significantly higher level of fatty acids in the plasma and the myocardial tissue, which can be harmful to the heart.[5] H-FABP may serve a protective function for the myocardial cells against oxidation of these fatty acids, while still having these substances readily available for the metabolic needs of the cell. During myocardial ischemia, H-FABP leaks out of myocardial tissue and can be detected in the blood as early as within 1 h after onset of chest pain, with peak values reached at 3–6 h and plasma levels returning to normal within 24–30 h.[4,5] The combination of initial H-FABP release after symptom onset, rapid kidney clearance from the circulation, and high cardiac specificity makes it an early cardiac marker for diagnosis of AMI and reinfarction. H-FABP is also potentially suitable for early estimation of infarct size due to its rapid and robust release into plasma after symptom onset and its rapid clearance from the circulation within 24 h.[5]

A one-step H-FABP immunotest, called CardioDetect®, is designed to detect H-FABP in whole blood samples, is now commercially available.[6–10] The test result is available within 15 min after addition of blood samples. It requires no sample pretreatment and thus can be applied in emergency situation.

The aim of the present study was to evaluate the diagnostic performances of H-FABP, Myo, cardiac troponin I (cTnI), and their combinations in patients presenting with chest pain and suspected of myocardial infarction.

METHODS

Participants

The study was reviewed and approved by the ethical committee of the FuWai Hospital in Beijing in April 2007. Patients presenting to the ED were consecutively screened for entry criteria: onset of symptoms suggestive of AMI from the last 1–6 h and age >18 years. Presenting symptoms typically included chest pain or discomfort at rest lasting for at least 10 min, but also atypical "vague" complaints such as abdominal discomfort, dizziness, or sudden onset of dyspnea. A total of 200 patients met these entry criteria. Patients unable to give consent, with chronic renal failure (CRF), the onset time of chest pain >6 h, and with AMI, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) within two weeks were excluded because these may cause elevated H-FABP levels.[11,12] Patients with no history of renal failure and serum creatinine level <130 μmol/L were defined as having normal renal function.

Specimen Processing

Blood samples were taken from each patient at admission and 2 h after admission together with routine blood sampling. Heparized blood samples were collected for the CardioDetect measurement and centrifuged for 5 min at 4000 rpm for cTnI and Myo measurements. The medical staff members were trained in performing and reading the CardioDetect. They were blinded to the standard diagnosis. At presentation, current symptoms and past medical history were documented using a predefined protocol. Follow-up information regarding standard diagnosis and outcome was extracted from medical notes and discharge letters.

Cardiac Markers

All patients underwent blood testing in the ED. cTnI and Myo were measured by chemiluminescent immunoassays using a Beckman Coulter Access II Analyzer (Beckman Coulter, California, USA) with the cut-off values at 0.1 μg/L (the 99th percentile cutoff with a CV < 10%) and 60 μg/L respectively. All patients were also tested with the CardioDetect H-FABP immunotest. It is a rapid chromatographic immunoassay designed for qualitative determination of H-FABP in blood samples with a cut-off value of 7 μg/L.

The test required 100–120 μL of sample, and the result was interpreted within 15 min after sample application. The test result was positive if two red lines were visible (one at the area of the test zone and one at the control zone). This indicated that the concentration of H-FABP in the sample was above the threshold value of 7 μg/L. The result was negative if only one red line was visible at the control zone. This reading indicated that the concentration of H-FABP in the sample was below the threshold value. The test was invalid if no line was visible or if a line only at the test zone was visible. In such a case, the measurement was repeated immediately. If H-FABP was negative at presentation, it would be tested again 2 h later together with Myo and cTnI. All of the patients would be tested with cTnI, CK-MB, Myo, and ECG 12–24 h from symptom onset in order to make the final diagnosis.

Standard Diagnosis

This clinical observation started before the update universal definition of myocardial infarction was published, so we still use the old one to determine AMI. The standard diagnostic protocol included 12-lead ECG and cardiac markers.[13] The diagnosis was made after critical review of patients' demographic data, clinical symptoms, ECG, laboratory data, and medical history. Diagnostic outcome was categorized into three groups by a senior cardiologist according to the Joint Guidelines of the European Society of Cardiology and American College of Cardiology Committee:[14] (i) ST-elevation myocardial infarction (STEMI), (ii) non-ST-elevation myocardial infarction (NSTEMI), (iii) and non-MI. AMI was defined when two of the following criteria fitted: (a) typical ischemic symptoms greater than 20 min, (b) new or recurrent ST segment elevation or depression >0.1 mv in >2 contiguous leads, (c) biochemical markers of myocardial necrosis including troponin I (the 99th percentile cutoff with a CV < 10%) and CK-MB to greater than 2 × ULN (the upper limit of normal).

Statistics

Data are presented as medians, interquartile ranges (IQR), and means ± standard deviation (SD). Diagnostic test criteria including sensitivity, specificity, and negative and positive predictive values were calculated by using MedCalc version 7.0 (MedCalc Software, Mariakerke, Belgium). The level of significance was set at $p < 0.05$.

RESULTS

Between 24 May 2007 and 14 February 2008, a total of 200 patients were enrolled in this study. Mean age was 61.4 ± 13.4 years (range: 33–88 years),

and 151 (75.5%) were male. Median time from symptom onset to first blood sample was 2.3 h (IQR 1.7–4.0 h). Patient characteristics are presented in Table 1. One hundred twelve patients (56%) were over 60 years old, 62 (31%) were smokers, and 198 (99%) presented with chest pain. Thirty-six patients (18%) had diabetes, 50 (25%) had hyperlipidemia, 107 (54%) had hypertension, and 74 (37%) had prior history of cardiovascular diseases.

Acute myocardial infarction was diagnosed in 107 (53.5%) individuals, of whom 93 (46.5%) had STEMI and 14 (7%) had NSTEMI. The non-MI group consisted of 93 patients with a final diagnosis of other coronary heart diseases or non-coronary heart diseases.

Diagnostic Performance of H-FABP Immunotest

Table 1 shows the diagnostic performances of H-FABP and H-FABP combined with cTnI at presentation. The overall sensitivity of the combination was better than that of H-FABP alone, but the inverse was observed for specificity. Better H-FABP test performance was found in elderly patients, smokers, and patients with prior history of cardiovascular diseases. Males had higher sensitivity but lower specificity than females. Patients with hypertension also had higher sensitivity but lower specificity, while patients with diabetes and hyperlipidemia had higher specificity but lower sensitivity. The combination test gave better diagnostic performance in patients with hypertension. The elderly patients, males, smokers, and patients with prior history of cardiovascular diseases had higher sensitivity but lower specificity. Patients with diabetes and hyperlipidemia had higher specificity but lower sensitivity.

Sensitivities and Specificities for Different Cardiac Markers

The diagnostic performances of different cardiac markers at admission and 2 h after admission are summarized in Table 2. The H-FABP immunotest was found to have a better sensitivity than the other cardiac markers and a better specificity than Myo at admission and 2 h after admission. The sensitivity and specificity for H-FABP of the patient samples taken at admission were 76.6% and 88.2%, respectively. Both sensitivity and negative predictive value (NPV) increased to over 90.0% at 2 h after admission, which were sufficient to safely allow ED discharge of non-AMI patients. The sensitivity and specificity for Myo were 72.9% and 86.0% at admission, respectively. Both values for Myo could not increase to over 90.0%, even at 2 h after admission. Although the specificity (90.3%) for cTnI remained high at

TABLE 1 Patient Characteristics and Diagnostic Performance of H-FABP at Presentation

			H-FABP				H-FABP +cTnI			
	Number (%)	AMI Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	200	107 (54)	76.6 (67.5–84.3)	86.0 (77.3–92.3)	86.3 (77.7–92.5)	76.2 (66.9–84.0)	85.1 (76.9–91.2)	81.7 (72.4–89.0)	84.3 (76.0–90.6)	82.6 (73.3–89.7)
Demographics										
Age (Years, mean ±SD)	61.4 ± 13.4									
≥60 years	112 (56)	55 (49)	85.5 (73.3–93.5)	87.7 (76.3–94.9)	87.0 (75.1–94.6)	86.2 (74.6–93.8)	90.9 (80.0–96.9)	80.7 (68.1–89.9)	82.0 (70.0–90.6)	90.2 (78.6–96.7)
<60 years	88 (44)	52 (63)	67.3 (52.9-79.7)	83.3 (67.2–93.6)	85.4 (70.8–94.4)	63.8 (48.5–77.3)	78.9 (65.3–88.9)	83.3 (67.2–93.6)	85.4 (70.8–94.4)	63.8 (48.5–77.3)
Sex										
Female	49 (24.5)	18 (37)	66.7 (41.0–86.6)	90.3 (74.2–97.8)	80.0 (51.9–95.4)	82.4 (65.5–93.2)	83.3 (58.6–96.2)	87.1 (70.1–96.3)	78.9 (54.4–93.8)	90.0 (73.1–97.8)
Male	151 (75.5)	89 (59)	78.7 (68.7–86.6)	83.9 (72.3–92.0)	87.5 (78.2–93.8)	73.2 (61.4–83.1)	85.4 (76.3–92.0)	79.0 (66.8–88.3)	85.4 (76.3–92.0)	79.0 (66.8–88.3)
Presenting symptom										
Chest pain										
Yes	198 (99)	107 (54)	76.6 (67.5–84.3)	85.6 (76.6–92.1)	86.3 (77.7–92.5)	75.5 (66.0–83.5)	85.1 (76.9–91.2)	81.1 (71.5–88.6)	84.3 (76.0–90.6)	82.0 (72.5–89.4)
No	2 (1)	0 (0)	–	–	–	–	–	–	–	–
Risk factors										
Current smoker										
Yes	62 (31)	41 (66)	78.1 (62.4–89.4)	90.5 (69.6–98.5)	94.1 (80.3–99.1)	67.9 (47.7–84.1)	85.4 (70.8–94.4)	81.0 (58.1–94.4)	89.7 (75.8–97.1)	73.9 (51.6–89.7
No	138 (69)	66 (48)	75.8 (63.6–85.5)	84.7 (74.2–92.1)	82.0 (70.0–90.6)	79.2 (68.5–87.6)	84.9 (73.9–92.5)	81.9 (71.1–90.0)	81.2 (69.9–89.6)	85.5 (75.0–92.8)
Diabetes mellitus										
Yes	36 (18)	18 (50)	66.7 (41.0–86.6)	88.9 (65.2 -98.3)	85.7 (57.2–97.8)	72.7 (49.8–89.2)	83.3 (58.6–96.2)	83.3 (58.6–96.2)	83.3 (58.6–96.2)	83.3 (58.6–96.2)
No	164 (82)	89 (54)	78.7 (68.7–86.6)	85.3 (75.3–92.4)	86.4 (77.0–93.0)	77.1 (66.5–85.7)	85.4 (76.3–92.0)	81.3 (70.7–89.4)	84.4 (75.3–91.2)	82.4 (71.8–90.3)
Hyperlipidemia										
Yes	50 (25)	22 (44)	63.6 (40.7–82.8)	92.9 (76.5–98.9)	87.5 (61.6–98.1)	76.5 (58.8–89.2)	77.3 (54.6–92.1)	89.3 (71.7–97.6)	85.0 (62.1–96.6)	83.3 (65.3–94.3)
No	150 (75)	85 (57)	80.0 (69.9–87.9)	83.1 (71.7–91.2)	86.1 (76.4–92.8)	76.1 (64.5–85.4)	87.1 (78.0–93.4)	78.5 (66.5–87.7)	84.1 (74.7–91.0)	82.3 (70.5–90.8)
Hypertension										
Yes	107 (54)	50 (47)	78.0 (64.0–88.5)	84.2 (72.1–92.5)	81.2 (67.4–91.0)	81.4 (69.1–90.3)	86.0 (73.3–94.2)	86.0 (74.2–93.7)	84.3 (71.2–93.0)	87.5 (75.9–94.8)
No	93 (46)	57 (61)	75.4 (62.2 -85.9)	88.9 (73.9–96.8)	91.5 (79.6–97.6)	69.6 (54.2–82.2)	84.2 (72.1–92.5)	75.0 (57.8–87.9)	84.2 (72.1–92.5)	75.0 (57.8–87.9)
Prior history of cardiovascular event										
Yes	74 (37)	30 (41)	73.3 (54.1–87.7)	77.3 (62.2–88.5)	68.7 (50.0–83.9)	81.0 (65.9–91.4)	90.0 (73.4–97.8)	75.0 (59.7–86.8)	71.1 (54.1–84.6)	91.7 (77.2–98.2)
No	126 (63)	77 (61)	77.9 (67.0–86.6)	93.9 (83.1–98.6)	95.2 (86.7–99.0)	73.0 (60.3–83.4)	83.1 (72.9–90.7)	87.8 (75.2–95.3)	91.4 (82.3–96.8)	76.8 (63.6–83.4)

PPV: positive predictive value; NPV: negative predictive value; H-FABP: heart-type fatty acid-binding protein; cTnI: cardiac troponin I.

TABLE 2 Sensitivities, Specificities, and Predictive Values of Different Cardiac Markers for Diagnosis of AMI

Cardiac Marker		Cut-off (μg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	−LR
H-FABP	At admission	7	76.6	88.2	87.6	76.2	6.49	0.27
	2 hours after admission		(67.5–84.3)	(79.8–93.9)	(79.0–93.7)	(66.9–84.0)	(5.60–7.60)	(0.10–0.50)
			94.4	81.7	84.1	92.4	5.16	0.07
			(88.2–97.9)	(72.4–89.0)	(75.8–90.5)	(84.2–97.1)	(4.60–5.80)	(0.03–0.20)
Myo	At admission	60	72.9	86.0	86.3	73.9	5.21	0.32
	2 hours after admission		(63.4–81.0)	(77.3–92.3)	(77.7–92.5)	(64.7–81.8)	(4.70–6.10)	(0.20-0.60)
			84.1	78.5	83.5	81.7	3.48	0.20
			(75.8–90.5)	(68.8–86.3)	(75.6–89.6)	(72.4–89.0)	(3.10–4.00)	(0.10-0.40)
cTnI	At admission	0.1	71.0	90.3	89.4	73.0	7.34	0.32
	2 hours after admission		(61.5–79.4)	(82.4–95.5)	(80.8–95.0)	(64.0–80.9)	(6.40–8.40)	(0.20–0.60)
			88.8	82.8	85.6	86.5	5.16	0.14
			(81.2–94.1)	(73.6–89.8)	(77.6–91.5)	(77.6–92.8)	(4.60–5.80)	(0.07–0.30)

PPV: positive predictive value; NPV: negative predictive value; H-FABP: heart-type fatty acid-binding protein; cTnI: cardiac troponin 1.

TABLE 3 Areas Under Receiver Operating Characteristic Curves of Different Cardiac Markers and their Combinations

	At admission	2 hours after admission
H-FABP	0.813 (0.751–0.876)	0.864 (0.808–0.920)
Myo	0.805 (0.742–0.868)	0.829 (0.769–0.890)
cTnl	0.807 (0.744–0.869)	0.858 (0.801–0.941)
H-FABP + cTnl	0.834 (0.774–0.894)	0.846 (0.787–0.906)
Myo + cTnl	0.819 (0.757–0.881)	0.835 (0.774–0.896)

H-FABP: heart-type fatty acid-binding protein; cTnI: cardiac troponin I; Myo: myoglobin.

admission, its sensitivity (71.0%) was still low, and both values also could not increase to over 90.0%, even at 2 h after admission.

Receiver Operating Characteristic Curves for Different Cardiac Markers

The areas under the receiver operator characteristic (ROC) curves to distinguish AMI from non-AMI for H-FABP were greater than those of the other cardiac markers at admission and 2 h after admission (Table 3). Thus, H-FABP has great potential as an excellent cardiac marker for diagnosis of AMI in the early phase.

At the time of ED presentation, the use of both early and late markers rather than the gold standard troponins alone increases the diagnostic performance. The area under the curve for the combination of H-FABP with cTnI was the greatest at admission [0.834 (95% CI: 0.774–0.894)].

DISCUSSION

No single cardiac marker used alone is ideal. Although troponins are the gold standard cardiac markers, they still fail in two important aspects: the ability to detect early AMI and reinfarction. In view of the poor troponin sensitivity in the early detection of myocardial injury within the first 6 h after the onset of symptoms, a cardiac multi-marker strategy is of particular value when the analytical sensitivity of the troponin detection method is unsatisfied. As shown in the current study, cTnI is less sensitive than H-FABP and Myo in the early stages of infarction. Interestingly, one advantage of troponins—their ability to detect cardiac damage up to several days after myocardial infarction—is also a disadvantage in detection of reinfarction. It is common for cardiologists to look for cardiac markers for detecting recurrences as a second or third cardiac event soon after an initial infarction. The quick clearance rate and release kinetic of H-FABP makes it an ideal

myocardial marker for the detection of reinfarction soon after the initial infarction.[4] Therefore, use of multiple markers as a cardiac panel has a better chance of meeting all requirements of an ideal cardiac marker.

The small molecular weight of H-FABP (15 kDa) favors its early release, due to the higher permeability of the endothelial barrier for small proteins. These characteristics, along with a low physiological concentration for the identification of myocardial damage, enable H-FABP to have an improved diagnostic capability when compared with other early cardiac markers, such as Myo, whose specificity for cardiac events is poor.

In this study, H-FABP was found to have a better sensitivity than the other cardiac markers and a better specificity than Myo at admission and 2 h after admission. Both sensitivity and NPV for H-FABP increased to over 90.0% at 2 h after admission to safely allow ED discharge. Chan et al.[4] also demonstrated that H-FABP reliably diagnosed AMI patients 1 h after admission, and 100% of non-AMI patients were excluded with no false negative results. The late markers cTnI and creatine kinase (CK) have similar diagnostic performance only 7 h later. Nakata et al.[3] also reported that H-FABP gave the greatest diagnostic and prognostic powers when compared to Myo, cTnT, and CK-MB within 12 h after the onset of symptoms.

The diagnostic performance of CardioDetect that we report is similar to that of in-hospital patients suspected of AMI[6,7,15] and patients with acute ischemic chest pain delivered by a mobile intensive care unit (MICU).[16] The use of the CardioDetect appears to be of unique value in the early stage of AMI. Indeed, the specificity of the CardioDetect in our study and the

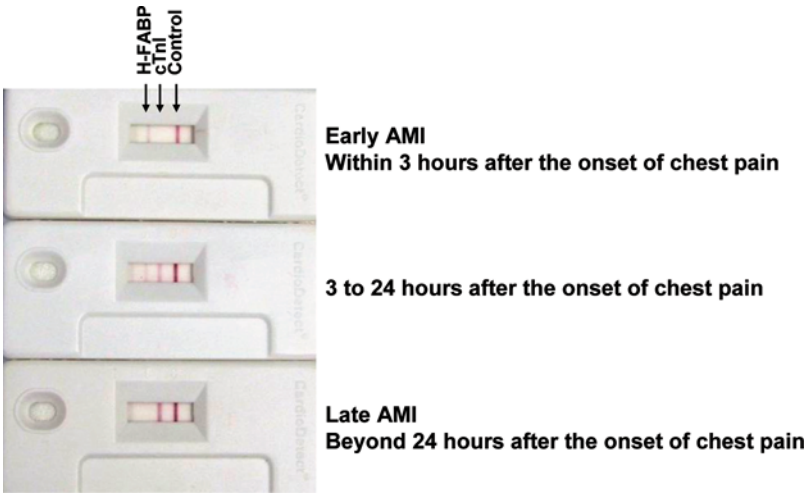

FIGURE 1 Lifesaver: CardioDetect Plus for simultaneous detection of heart-type fatty acid binding (H-FABP) and cardiac troponin I (cTnI) to cover the whole diagnostic window for diagnosis of early and late acute myocardial infarction (AMI).

previous studies was found to be comparable to that of repeated troponin measurements, but with a much greater sensitivity in the early stage of AMI. The result of the CardioDetect can not only be assessed visually with the naked eye, but also can be quantified by means of a reading device. A good agreement between the CardioDetect and the conventional enzyme-linked immunosorbent assay (ELISA) was found in previous studies.[6,10]

No single marker satisfies all requirements of the ideal marker; therefore, a panel consisting of H-FABP and troponin is recommended. Patients presenting very early (less than 2 to 3 h after symptom onset) may have elevations in H-FABP in the absence of cTnI elevations. When cTnI is elevated in the absence of an H-FABP elevation, it is usually a delayed presentation. Most typically, discordant results are helpful to the clinician because they can identify a high-risk patient who may be missed if only one marker is tested.

The current study shows that a combination of H-FABP and cTnI gave the greatest area under the curve at admission and thus was the most effective diagnostic tool for diagnosis of AMI. Mion et al.[17] also demonstrated that the combination of cTnI and H-FABP gave the greatest diagnostic efficacy in AMI diagnosis. This strategy may allow the complete detection of cardiac injury. However, the assay time required for the Evidence® Cardiac Panel is too lengthy for its use in ED, exceeding the 60 min recommended by the National Academy of Clinical Biochemistry (NACB) guidelines for turnaround time for cardiac markers. Therefore, a novel approach by integrating H-FABP and cTnI into one test is being developed (Figure 1). This approach may improve the diagnosis of AMI on the initial sample. However, further investigation is required.

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