Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism

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Aims We investigated the value of a novel early biomarker, heart-type fatty acid-binding protein (H-FABP), in risk stratification of patients with acute pulmonary embolism (PE).

Methods and results We prospectively included 107 consecutive patients with confirmed PE. The endpoints were (i) PE-related death or major complications and (ii) overall 30-day mortality. Overall, 29 patients (27%) had abnormal (>6 ng/mL) H-FABP levels at presentation. Of those, 12 (41%) had a complicated course, whereas all patients with normal baseline H-FABP had a favourable 30-day outcome (OR, 71.45; P < 0.0001). At multivariable analysis, H-FABP (P < 0.0001), but not cardiac troponin T (P = 0.13) or N-terminal pro-brain natriuretic peptide (P = 0.36), predicted an adverse outcome. Evaluation of a strategy combining biomarker testing with echocardiography revealed that patients with a negative H-FABP test had an excellent prognosis regardless of echocardiographic findings. In contrast, patients with a positive H-FABP test had a complication rate of 23.1% even in the presence of a normal echocardiogram, and this rose to 57.1% if echocardiography also demonstrated right ventricular dysfunction (OR vs. a negative H-FABP test, 5.6 and 81.4, respectively).

Conclusion H-FABP is a promising early indicator of right ventricular injury and dysfunction in acute PE. It may help optimize risk stratification algorithms and treatment strategies.

Introduction

Data from earlier studies¹ and a number of recent reports² point to right ventricular dysfunction as an important determinant of outcome in patients with acute pulmonary embolism (PE). Consequently, early diagnosis of a failing right ventricle is generally viewed as a critical step in contemporary risk stratification and management of PE. Beyond clinical assessment of overt haemodynamic instability, or imaging of right ventricular dimensions and function using echocardiography³ or chest CT,⁴,⁵ interest currently focuses on the prognostic value of cardiac biomarkers. Several studies⁶ could convincingly demonstrate that the absence of cardiac troponin elevation can exclude an adverse in-hospital outcome with a high negative predictive value (NPV). However, both in patients with acute coronary syndromes⁷ and in those with acute PE,⁸,⁹ cardiac troponin elevation may not occur until 6–12 h after the onset of symptoms. Consequently, repeated troponin measurements over the first 24 h of hospitalization may be necessary for reliable risk assessment.⁶,¹⁰ Brain natriuretic peptides are highly sensitive indicators of neurohormonal activation resulting from ventricular dysfunction, and they can also be used to exclude a high mortality and complication risk in the acute phase of PE.⁸ However, their limitations include even lower prognostic specificity compared with troponins⁶ and the lack of prospectively tested cutoff levels.¹¹

Fatty acid-binding proteins (FABPs) are relatively small cytoplasmic proteins (12–15 kDa) that are abundant in tissues with active fatty acid metabolism, including the heart.¹² In fact, heart-type FABP (H-FABP) is particularly important for myocardial homoeostasis, since 50–80% of the heart’s energy is provided by lipid oxidation, and H-FABP ensures intracellular transport of insoluble fatty acids.¹³ Following myocardial cell damage, this small protein diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 min after symptom onset, reaching its peak within 6 h.¹³ These features make H-FABP an excellent candidate marker of myocardial injury,¹⁴ and very recent data suggest that it may indeed provide prognostic information superior to that of cardiac troponins in the early stages of PE.
hours of acute coronary syndromes. Acute submassive or massive PE also results in early damage to the (right ventricular) myocardium, but it has never been tested whether H-FABP might be useful as an early, specific indicator of poor prognosis in the acute phase of PE. Therefore, in the present study of 107 consecutive patients with acute PE, we examined the ability of H-FABP to predict or exclude an unfavourable in-hospital outcome and compared its prognostic value with that of other cardiac biomarkers, particularly cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods

Patient population and study design

Between September 2003 and October 2005, we prospectively studied 107 consecutive patients (67 women; age 61 ± 16 years) with confirmed acute PE. Patients presenting at the emergency department of a university hospital with high clinical probability of PE,17 or with low/intermediate probability and a positive D-dimer ELISA test (>500 μg/L), underwent sonographic or phlebographic examination of the leg veins, contrast-enhanced CT pulmonary angiography, ventilation-perfusion lung scan, or (rarely) conventional pulmonary angiography, alone or in combination, to confirm acute PE. Following diagnosis of PE, transthoracic echocardiography was performed to detect (or exclude) right ventricular dysfunction, i.e. dilatation of the right ventricle (end-diastolic diameter >30 mm from the parasternal view, or the right ventricle appearing larger than the left ventricle from the subcostal or apical view) combined with right atrial hypertension (absence of inspiratory collapse of the inferior vena cava) in the absence of left ventricular or mitral valve disease. Patients were excluded from the study if PE was an accidental finding obtained at diagnostic workup for another suspected disease.

Complete data on baseline parameters and the patients' treatment and outcome were obtained using a standardized questionnaire by investigators blinded to biomarker levels. The study design was observational, and biomarker levels were not used to guide patient management or to monitor the effects of treatment. The study protocol was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Definition of primary and secondary endpoints

The predetermined primary endpoint was a complicated 30-day outcome, defined as PE-related death or at least one of the following major adverse events: need for catecholamine administration (except for dopamine at the rate of 5 μg/kg/min) to maintain adequate tissue perfusion and prevent or treat cardiogenic shock; endotracheal intubation; and cardiopulmonary resuscitation. The secondary endpoint was overall (PE-related and PE-unrelated) mortality.

Biomarker testing

Venous plasma and serum samples were obtained on admission as well as 4, 8, and 24 h later, and were immediately stored at –80°C. Samples were later analysed in batches after a single thaw. cTnT (in serum samples) and NT-proBNP levels (in plasma samples) were determined with the use of a quantitative electrochemiluminescence assay (Elecys 2010 analyser, Roche Diagnostics) as described. For cTnT, a reference value of 0.04 ng/mL was used to distinguish between normal and elevated levels as proposed by the manufacturer. For NT-proBNP, the prognostically relevant cutoff level was prospectively set at 1000 pg/mL, a value corresponding to that recently determined in our centre by receiver operating characteristic (ROC) analysis.

Plasma levels of H-FABP on admission (dilution 1:5) were measured by a solid-phase ELISA based on the sandwich principle (HyCult Biotechnology, Uden, The Netherlands). According to the information provided by the manufacturer, this kit uses two monoclonal antibodies directed against different specific epitopes on the FABP molecule and shows no cross-reactivity with human intestinal-type or human liver-type FABP. The minimum measurable concentration is 100 pg/mL (standard curve from 100 to 25 000 pg/mL). The upper reference limit was prospectively set at 6 ng/mL in accordance with the findings of previous studies. The investigator who determined the biomarker levels was unaware of the patients' baseline parameters or clinical course. To avoid treatment bias, H-FABP concentrations were not communicated to the clinicians caring for the study patients.

Statistical analysis

At the time this study was designed, no data were available on the possible prognostic value of H-FABP in patients with PE. Therefore, the sample value of approximately 100 patients was chosen based on our previous publications, which had demonstrated that this sample size is adequate for demonstrating the prognostic value of other biomarkers in PE including, for example, troponins and NT-proBNP. Continuous variables were compared using Student’s t test, categorical variables with Fisher’s exact test. The prognostic relevance of the markers with respect to both the primary and the secondary endpoints was estimated both univariably and multivariably using an exact logistic regression model. In this model, dichotomized versions of the three biomarker variables of interest were primarily used. The cutoff values were prospectively chosen based on existing evidence as explained above. Linearity of the effect of continuous marker variables was verified by means of likelihood ratio tests comparing the linear continuous model with other models. In addition, ROC curves of H-FABP levels on admission, maximal troponin T concentrations over the first 24 h, and NT-proBNP levels on admission were calculated with the corresponding area under curve (AUC) values. For the multivariable analysis, the three biomarker variables (H-FABP, troponin T, and NT-proBNP) were entered into the model simultaneously. Additional (e.g. clinical) variables were not assessed in this model because of the relatively small sample size. Again, the results are presented as exact odds ratios (OR) with corresponding 95% confidence intervals (CI). In order to verify the validity of these calculations, we further applied a logistic regression model that used continuous versions of the biomarker values. In this latter model, OR and 95% CI were calculated for H-FABP increases by 1 ng/mL, troponin T increases by 0.01 ng/mL, and NT-proBNP increases by 1000 pg/mL. Linearity of the effect of continuous marker variables was verified by means of likelihood ratio tests comparing the linear continuous model with other models. In addition, ROC curves of H-FABP levels on admission, maximal troponin T concentrations over the first 24 h, and NT-proBNP levels on admission were calculated with the corresponding area under curve (AUC) values. For the multivariable analysis, the three biomarker variables (FABP, troponin T, and NT-proBNP) were entered into the model simultaneously. Additional (e.g. clinical) variables were not assessed in this model because of the relatively small sample size. Again, the results are presented as exact OR with corresponding 95% CI. All tests were two-sided and used a significance level of 0.05.

Results

Between September 2003 and October 2005, 240 consecutive patients with high clinical probability of PE, or with low/intermediate probability and a positive D-dimer ELISA test (>500 μg/L), underwent initial assessment at the emergency department of our university hospital for possible inclusion in the study. After obtaining preliminary consent from the patients, blood was drawn for determining the baseline (admission) levels of biomarkers prior to further diagnostic workup. PE was confirmed in 111 (46%) of the screened patients, four of whom refused to sign the written informed consent form and were excluded from further analysis. All patients in whom the diagnosis of PE was rejected were also excluded and their blood probes discarded. Thus, the final study population comprised 107 patients (67 women, 40 men; age 61 ± 16 years). In these
patients, acute PE was diagnosed by sonographic or phlebographic examination of the leg veins (62 patients; 58%), contrast-enhanced CT pulmonary angiography (63 patients; 59%), ventilation-perfusion lung scan (38 patients; 36%), or conventional pulmonary angiography (three patients; 2.8%), alone or in combination. All study patients had a complete echocardiographic examination.

The clinical symptoms and relevant findings of the study patients on admission are shown in Table 1. H-FABP concentrations ranged between 0.42 and 218 ng/mL, and 29 patients (27%) had abnormally elevated (>6 ng/mL) FABP at presentation. Of note, cTnT was initially elevated in only 13 (45%) of these patients. However, cTnT levels rose over the first 24 h of the hospital stay, and, eventually, 23 (80%) of the patients with initially elevated FABP also exhibited increased cTnT concentrations. Consequently, the correlation between H-FABP and cTnT elevation improved further when maximal (as opposed to baseline) troponin levels were taken into consideration ($P_{0.0001}$ vs. $P_{0.003}$). Abnormal H-FABP levels also correlated with NT-proBNP elevation ($P=0.006$).

During the hospital stay, 12 patients (11.2% of the study population) developed major PE-related complications (as defined in the Methods), and 10 of these patients died. Another patient died of cancer (in total, 11 deaths; mortality rate 10.3%). As shown in Figure 1A, H-FABP levels on admission overall were several-fold higher in patients who met the primary endpoint than in those with a favourable outcome, with almost no overlap between the two groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All study patients ($n=107$)</th>
<th>FABP $&gt;6$ ng/mL ($n=29$)</th>
<th>FABP $&lt;6$ ng/mL ($n=78$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported symptom onset $&lt;$24 h before presentation</td>
<td>62 (57.9%)</td>
<td>17 (58.6%)</td>
<td>45 (57.7%)</td>
<td>0.894</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>96 (89.7%)</td>
<td>24 (82.7%)</td>
<td>72 (93.3%)</td>
<td>0.277</td>
</tr>
<tr>
<td>Syncope</td>
<td>21 (19.6%)</td>
<td>10 (34.5%)</td>
<td>11 (14.1%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Haemodynamic instability$^a$</td>
<td>10 (9.3%)</td>
<td>9 (31.0%)</td>
<td>1 (1.3%)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Recent surgery (within 14 days)</td>
<td>18 (16.8%)</td>
<td>3 (10.3%)</td>
<td>15 (19.2%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Recent major trauma (within 14 days)</td>
<td>5 (4.7%)</td>
<td>2 (6.9%)</td>
<td>3 (3.8%)</td>
<td>0.881</td>
</tr>
<tr>
<td>History of venous thrombosis</td>
<td>33 (30.8%)</td>
<td>6 (20.7%)</td>
<td>27 (34.6%)</td>
<td>0.250</td>
</tr>
<tr>
<td>History of PE</td>
<td>17 (15.9%)</td>
<td>2 (6.9%)</td>
<td>15 (19.2%)</td>
<td>0.202</td>
</tr>
<tr>
<td>Cancer</td>
<td>20 (18.7%)</td>
<td>4 (13.8%)</td>
<td>16 (20.5%)</td>
<td>0.608</td>
</tr>
<tr>
<td>cTnT on admission $&gt;0.04$ ng/mL</td>
<td>27 (25.5%)</td>
<td>13 (44.8%)</td>
<td>14 (17.9%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximum cTnT $&gt;0.04$ ng/mL$^a$</td>
<td>39 (36.4%)</td>
<td>23 (79.3%)</td>
<td>16 (20.5%)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>NT-proBNP on admission $&gt;1000$ pg/mL</td>
<td>53 (51.5%)</td>
<td>21 (72.4%)</td>
<td>32 (41.0%)</td>
<td>0.008$^b$</td>
</tr>
<tr>
<td>Right ventricular dysfunction (echocardiography)</td>
<td>38 (36.4%)</td>
<td>16 (53.9%)</td>
<td>20 (29.9%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

$^a$Out of four measurements over the first 24 h.

$^b$Persistent hypotension, i.e. systolic blood pressure $<90$ mmHg or a fall in systolic blood pressure by $\geq40$ mmHg for at least 15 min, accompanied by signs of organ hypoperfusion.

Figure 1  H-FABP (A), troponin T (B), and NT-proBNP levels (C) on admission in patients who suffered major PE-related complications as opposed to those without a complicated 30-day outcome. For every biomarker, boxes indicate the 25th and 75th percentiles and horizontal lines show the median. Whiskers indicate the highest and lowest levels measured in the study population.
In comparison, although mean baseline concentrations of troponin T and NT-proBNP also were significantly higher in patients who subsequently developed major complications, there was clearly more overlap between the values of patients with a benign and those with a poor outcome (Figure 1, compare panels B and C with panel A). Of the 29 patients with H-FABP >6 ng/mL on admission, 12 (41%) had a complicated course, while none of those with normal baseline H-FABP experienced PE-related complications. This was translated into a very high risk for major complications in case of a positive test (OR, 71.5; 95% CI, 11.0–799.9; \( P < 0.0001 \)).

The relation between initial H-FABP elevation and both endpoints of the study is summarized in Figure 2A. The NPV of H-FABP elevation with regard to the primary endpoint was 100% and the positive predictive value (PPV) was 41% (prognostic sensitivity, 100%; specificity, 82%). Of note, one patient with normal H-FABP levels on admission died during the hospital stay, but the cause of his death was PE-unrelated (cancer).

Elevation of cTnT on admission also predicted a complicated 30-day outcome (OR, 8.86; 95% CI, 1.89–56.9; \( P = 0.003 \)), but the NPV of cTnT elevation on admission was lower (95%) compared with that of H-FABP and the PPV only 29%. The relation between initial cTnT elevation and both endpoints of the study is summarized in Figure 2B. The sensitivity of cTnT improved when the maximal troponin levels over the first 24 h (instead of the baseline concentrations) were taken into consideration (OR, 30.3; 95% CI, 4.69–799.9; \( P < 0.0001 \)), but its PPV remained lower than that of H-FABP (30 vs. 41%). Finally, NT-proBNP levels above the calculated cutoff value of 1000 pg/mL on admission were highly sensitive in predicting an adverse outcome (OR, 11.78; 95% CI, 1.60–527.0; \( P = 0.007 \)), but their PPV was very low (19%) in agreement with previous reports.6,8 The relation between initial NT-proBNP elevation and the endpoints of the study is shown in Figure 2C. Of note, logistic regression analysis considering continuous elevation in the concentration of the three biomarkers (instead of the predefined cutoff levels presented above) yielded comparable results regarding their impact on 30-day outcome. The ROC curves of the three biomarkers are shown, together with the corresponding c values, in Figure 3. H-FABP on admission yielded the largest area under the curve.

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When the three biomarkers were directly compared using multivariable logistic regression analysis, H-FABP (OR, 36.74; \( P < 0.001 \)).
95% CI, 5.14–999.9; P < 0.0001) but not cTnT (P = 0.13) or NT-proBNP (P = 0.36) on admission was identified as a significant predictor of a complicated 30-day outcome. Similar results were obtained with regard to the secondary endpoint of overall mortality (P = 0.001, P = 0.60, and P = 0.98, respectively). In fact, H-FABP remained superior to cTnT or NT-proBNP as a prognostic indicator even when the maximal levels of the latter biomarkers over the first 24 h were entered into the multivariable model.

As recent findings suggest that biomarker testing followed, if necessary, by echocardiography may represent a more rational and effective approach to risk stratification followed, if necessary, by echocardiography may represent a more rational and effective approach to risk stratification if patients with acute PE than either method used alone.6,8,21 We evaluated the prognostic value of H-FABP in combination with echocardiography in our patient population. Overall, 97 patients (91%) had baseline echocardiograms of adequate quality to permit diagnosis or exclusion of right ventricular dysfunction. All patients with a negative H-FABP test remained free of major complications regardless of the presence (n = 22) or absence (n = 48) of right ventricular dysfunction on echocardiography. Thus, a negative H-FABP test alone might have been capable of ruling out an adverse outcome in patients with acute PE. On the other hand, complication rates in patients with a positive H-FABP test were 23.1% in combination with a normal echocardiogram (n = 13; OR compared with a negative H-FABP test, 24.0; 95% CI, 2.4–999.9; P = 0.0062), and increased more than two-fold (57.1%) in those with echocardiographic evidence of right ventricular dysfunction (n = 14; OR, 106.2; 95% CI, 14.5–999.9; P < 0.0001). Compared with a single (PE-unrelated) death among the H-FABP-negative patients, overall mortality rates in H-FABP-positive patients were 7.7% (OR compared with a negative H-FABP test, 5.6; 95% CI, 0.07–458.0; P = 0.58) and 57.1% (OR, 81.4; 95% CI, 8.8–999.9; P < 0.0001) in the presence of a normal and an abnormal echocardiogram, respectively. Thus, a positive H-FABP test followed by evidence of RV dysfunction on echocardiography might have been capable of ruling in an adverse outcome in patients with acute PE.

**Discussion**

Cardiac biomarkers have been successfully used in the diagnosis of acute coronary syndromes and congestive heart failure for several years, but it was only recently that they were introduced into the management of patients with acute PE. In particular, the cardiac troponins I and T, and the brain natriuretic peptides BNP and NT-proBNP have demonstrated high sensitivity in the detection of right ventricular myocardial damage and/or dysfunction, and they appear capable of practically excluding a high risk of PE-related complications or death in the acute phase. When the two biomarkers were directly compared, NT-proBNP offered the advantage of superior prognostic sensitivity compared with cTnT and thus appeared more suitable for ruling out an adverse outcome.6 However, the positive prognostic value of elevated natriuretic peptide levels is disappointingly low.6 Furthermore, and importantly, the appropriate cutoff levels for distinguishing between a ‘positive’ and a ‘negative’ NT-proBNP test remain rather arbitrary as they have not yet been prospectively tested.11 Cardiac troponins do not share these latter limitations and are widely established in clinical practice, but their detection in the circulation may require that several hours elapse after the onset of symptoms.7,9 Therefore, the troponin levels measured on admission may not suffice to assess the prognosis and guide early therapeutic decisions. These facts indicate that novel biomarkers and algorithms need to be tested for more efficient and, particularly, faster risk assessment of acute PE.

The present study examined the prognostic value of a novel biomarker, H-FABP, in 107 consecutive patients with acute PE. Measurement of this small protein in the circulation, which is based on sandwich ELISA using two monoclonal antibodies (studies reviewed)13, recently yielded very promising results in the early diagnosis of myocardial injury due to acute coronary syndromes.14–16 We could now show that abnormally elevated, i.e. >6 ng/mL, plasma levels of H-FABP on admission were very reliable predictors of the outcome in 107 consecutive patients with PE, and their prognostic value appeared superior to that of cTnT and NT-proBNP. In particular, there was almost no overlap between patients who subsequently suffered major complications and those with an uncomplicated course with regard to baseline H-FABP concentrations, and none of the patients with initially normal H-FABP levels had a complicated 30-day outcome or died of PE-related causes. These findings resulted in an excellent negative prognostic value of 100%, which was paralleled by that of cTnT only when the maximum (instead of the initial) concentrations of the latter biomarker were taken into consideration. Importantly, the PPV (41%) of H-FABP, an indicator of the biomarker’s cardiосpecificity, also was superior to that of cTnT (29%) and NT-proBNP (19%). In fact, H-FABP, but not cTnT or NT-proBNP, remained a highly significant predictor of adverse outcome when the three biomarkers were compared by multivariable analysis. Moreover, analysis of H-FABP in combination with echocardiography revealed that cardiac ultrasound offered no additional prognostic information in the presence of a negative H-FABP test. On the other hand, in patients with H-FABP >6 ng/mL on admission (27% of the entire study population), complication rates doubled and the relative risk of an adverse outcome was four times higher in the presence of right ventricular dysfunction on echocardiography. However, before H-FABP can replace existing biomarkers in risk stratification algorithms aimed at detecting high-risk patients with submassive PE, our findings in an unselected patient population need to be confirmed by larger studies focusing on normotensive patients with acute PE. In addition, it remains to be shown whether, and to what extent, H-FABP elevation may accompany right ventricular dysfunction resulting from congestive heart failure or idiopathic pulmonary hypertension.

H-FABP testing offers a number of theoretical and practical advantages for the detection of myocardial injury. These are related to (i) its small molecular size, which results in favourable kinetics of the assay (very early release after injury); (ii) its relative tissue (myocardial) specificity, which resembles that of the MB isoenzyme of creatine kinase; and (iii) its confinement to the cytoplasmic space.13 In fact, the release characteristics of H-FABP from injured myocardium closely resemble those of myoglobin, the most sensitive marker of myocardial injury currently in use.14 However, the cardiac tissue content of H-FABP is higher than that of myoglobin and the plasma levels lower, which makes H-FABP an even more sensitive marker than...
myoglobin. Moreover, and importantly, H-FABP is more cardiосpecific than myoglobin, since the skeletal muscle content is only 10–30% of that found in cardiac muscle, whereas the skeletal muscle content of myoglobin is approximately twice as high as that of cardiac muscle. Nevertheless, some data suggest that the applicability of H-FABP assays could be limited in patients with skeletal muscle damage, possibly including those who undergo electric cardioversion or cardiopulmonary resuscitation. In addition, H-FABP levels may have lower specificity in patients with renal failure.

In the present study, H-FABP levels were measured using solid-phase ELISA based on the sandwich principle. Qualitative lateral-flow assays (whole blood tests) may simplify H-FABP testing and allow reporting of normal or elevated H-FABP levels (with a cutoff value of 6 ng/mL) within 15 min. The clinical usefulness of this latter approach will require further testing in patients with acute myocardial ischaemia or PE.

In conclusion, the results of the present study, together with those of a very recent report, suggest that H-FABP might be a particularly promising early indicator of right ventricular dysfunction and damage in acute PE. Thus, the role of cardiac biomarkers in diagnosis and risk stratification continues to evolve, and their importance keeps growing, not only in the setting of acute coronary syndromes but also in acute PE. Novel biomarkers such as H-FABP will hopefully improve prediction of the patients’ risk and optimize treatment strategies by promptly identifying candidates for urgent medical (thrombolysis), surgical, or catheter-based recanalization.

Conflict of interest: none declared.

References