NT-proBNP Levels in Patients with Non-ST-segment Elevation Acute Coronary Syndrome

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Abstract

Background: Non-ST-segment elevation acute coronary syndrome is associated with elevation of brain natriuretic peptide and markers of myocardial necrosis, although its relationship with the TIMI score and left ventricular function are largely unknown.

Objective: To evaluate the correlation between plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and markers of myocardial necrosis [creatine phosphokinase muscle-brain fraction (CK-MB) and troponin I], TIMI risk score and left ventricular ejection fraction in patients with non-ST-segment elevation acute coronary syndrome.

Methods: Eighty-seven patients with non-ST-segment elevation acute coronary syndrome were divided into two groups: 37 (42.5%) with unstable angina and 50 (57.5%) with non-ST-segment elevation myocardial infarction.

Results: Left ventricular ejection fraction more than 40% was found in 86.2% of the total sample. Serum levels of NT-proBNP was higher in patients with non-ST elevation myocardial infarction than in those with unstable angina (p<0.001). Increased levels of NT-proBNP were associated with increases in troponin I (rs=0.425, p<0.001), peak CK-MB (rs=0.458, p<0.001) and low left ventricular ejection fraction (rs=-0.345, p=0.002); no correlation was found with the TIMI risk score (rs=0.082, p=0.44). Multivariate analysis revealed that left ventricular ejection fraction and troponin I levels were independently correlated with NT-proBNP levels (p=0.017 and p=0.002, respectively).

Conclusion: Increased levels of NT-proBNP in patients with non-ST-segment elevation acute coronary syndrome are not related exclusively to low left ventricular ejection fraction, but can also be caused by the presence of myocardial ischemia and necrosis. (Arq Bras Cardiol. 2011; [online].ahead print, PP.0-0)

Keywords: Acute coronary syndrome; natriuretic peptides; myocardial infarction; angina, unstable.

Introduction

Determining the concentration of circulating natriuretic peptides is important in the diagnostic and prognostic evaluation of patients with acute coronary syndrome (ACS)1,2. In ACS patients with ST-segment elevation myocardial infarction (STEMI), natriuretic peptides can be used to detect left ventricular dysfunction and are powerful independent predictors of death, heart failure and further myocardial infarctions1,3.

Several studies have consistently associated increased plasmatic levels of brain natriuretic peptides (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) with poor long-term prognosis in NSTE-ACS patients4-8. However, those studies have not excluded patients with left ventricular dysfunction, a condition secondary to NSTE-ACS that, by itself, is known to increase BNP and NT-proBNP levels; as a result, the real role of high levels of natriuretic peptides as markers of ischemia and necrosis on the prognosis of NSTE-ACS remains uncertain.

The objective of this study was to assess plasma NT-proBNP levels in NSTE-ACS inpatients without heart failure, and to correlate these findings with other markers of myocardial necrosis (CK-MB and troponin I), TIMI risk score and left ventricular ejection fraction (LVEF).

Methods

Study Group

This observational, cross-sectional study was conducted at Hospital Socor, Belo Horizonte, MG, Brazil. Eighty-seven patients with suspicion of NSTE-ACS admitted to the intensive care unit (ICU) were consecutively selected and followed up until discharge. Inclusion criteria were age over 18 years, established diagnosis of NSTE-ACS, and admission within less than 72 hours after the onset of symptoms. Patients who refused or were unable to participate in the study, or who presented one of the following conditions, were excluded: renal failure (serum creatinine > 2.5 mg/dL),
preexisting valvular disease, hypertrophic cardiomyopathy, severe systemic hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg), cardiogenic shock, refractory ventricular arrhythmia, recent acute myocardial infarction (< four weeks prior to hospitalization), recent myocardial revascularization surgery (< four weeks), recent percutaneous coronary intervention (< two weeks), previous diagnosis or signs/symptoms of congestive heart failure, severe non-cardiovascular disease limiting life expectancy, previous transplant of vital organs (lungs, liver, heart, and kidneys) or patients on transplant waiting lists. All patients included in the study signed an informed consent form. The study protocol was approved by the Research Ethics Committees of Universidade Federal de Minas Gerais and Hospital Socor, Belo Horizonte, Brazil.

Clinical and electrocardiographic data

Clinical data and information on previous conditions or interventions, risk factors for coronary artery disease (CAD) and medications in use were collected during each patient’s stay in the ICU. Electrocardiograms were performed to assess ST-segment and T-wave abnormalities.

Diagnosis of unstable angina was confirmed based on the presence of at least one of the three features: (i) typical and prolonged (> 20 minutes) chest pain at rest; (ii) new-onset angina of at least class III severity according to the Canadian Cardiovascular Society (CCS); and (iii) increasing angina previously diagnosed and becoming more frequent, longer in duration or lower in threshold; any of these findings should be associated with absence of increased markers of myocardial necrosis (CK-MB and troponin I), with or without ST-segment or T-wave abnormalities on electrocardiogram. NSTEMI was defined as the presence prolonged chest pain (> 20 minutes) associated with increased CK-MB or troponin I levels (the presence of increased troponin levels only, without a CK-MB increase, was also considered diagnostic), with or without electrocardiographic abnormalities. Electrocardiographic findings were classified as T-wave abnormalities, ST-segment depression or transitory ST-segment elevation in at least in two contiguous leads.

Treatment and laboratory routines followed the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) for the management of patients with unstable angina and NSTEMI.

Laboratory data

CK-MB measurements were performed using the Cobas Mira Plus system (Roche Diagnostics GmbH, Mannheim, Germany), at baseline and at 8 and hours 16 after admission. CK-MB results were expressed in UI/L (reference value: < 10UI/L). Troponin I levels were measured using a chemiluminescence method on the Immulite® system (DPC, New Jersey, USA), usually on admission. The reference limit recommended by the manufacturer was < 1.0 ng/mL.

Plasma NT-proBNP concentration was determined by electrochemiluminescence using an Elecsys 2010/Modular Analytics E170 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Blood samples were collected in a tube without anticoagulants within 72 hours after the onset of symptoms, with the patient resting quietly while semirecumbent. Samples were centrifuged at 3,000 revolutions per minute during 10 minutes and the serum was extracted. NT-proBNP results were expressed in pg/ml.

The TIMI risk score (thrombolysis in myocardial infarction) was used for risk stratification, as previously described.

Doppler Echocardiography

Doppler echocardiography was performed using a 5500 Phillips system (Phillips Medical Systems, Washington, USA). Two investigators performed and analyzed all the tests and both were blinded to patients’ clinical data. Both investigators evaluated the exams and disagreements were solved by consensus. The area-length method was used to determine ejection fraction.

Statistical analysis

Sample size was calculated to find a correlation (r) of at least 0.3 between NT-proBNP levels and necrosis markers (CK-MB and troponin I), considering a significance level of 0.05 and a power of 0.80 in a two-sided test.

Qualitative variables were described in terms of frequency; quantitative variables were presented as measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range, IQR). The distribution of continuous variables was tested for normality, and mathematical transformations were carried out when necessary. Comparisons between groups were carried out using Student’s t-test (variables with normal distribution) or nonparametric tests. The correlation between NT-proBNP and troponin I, CK-MB, TIMI risk score and LVEF was analyzed using Pearson’s or Spearman’s correlation coefficient. Statistical significance was set at 0.05.

A multivariate analysis was carried out to assess whether the relationship between the markers of myocardial necrosis and NT-proBNP levels was independent of ejection fraction. The partial correlation coefficient found between necrosis markers and NT-proBNP levels was evaluated using Pearson’s method, adjusted to ejection fraction. A multiple linear regression analysis was also performed to test for residual normality, where the natural logarithm (ln) NT-proBNP was the dependent variable, and LVEF and levels of necrosis markers were the independent variables.

Results

Clinical data

Clinical characteristics are shown in Table 1. Patients were divided into two groups according to the diagnosis: (i) unstable angina (troponin I < 1.0 ng/ml), 37 patients (42.5%), and (ii) NSTEMI (troponin I ≥ 1.0 ng/ml), 50...
patients (57.5%). The mean age of the 87 patients was 61.1 (±11.4) years and it was similar in the two groups; there was a predominance of male patients (64.4%). Most patients were using aspirin (97.7%) and clopidogrel (95.4%). A great number of NSTEMI patients had been treated with glycoprotein IIb/IIIa inhibitors (n = 36, 72.0%), whereas only three (8.1%) of the group with unstable angina (p < 0.001) had received this medication. Fifty-two patients (60.5%), mostly from the NSTEMI group (n = 40, 76.9%), were submitted to coronary angiography during their stay at the ICU.

Events were rare among NSTEMI patients during hospital stay: one death due to cardiogenic shock, two patients with refractory angina, one with acute pulmonary edema, and one with supraventricular tachycardia; in the unstable angina group, only one patient presented acute atrial fibrillation.

Electrocardiographic data

More than half of the patients (n = 49, 58.3%) did not present electrocardiographic ST-segment and T-wave abnormalities that could be associated with ischemia. Electrocardiographic abnormalities were found in 35 (41.7%) patients: ST-segment abnormalities (transitory depression or elevation) in 18 (21.4%), and T wave abnormalities in 17 (21.3%) (Table 2).

Laboratory data

Laboratory results were similar in both groups. Median creatinine was 0.9mg/dL (IQR=0.3), the highest value being 2.0mg/dL (Table 3).

Median (IQR) levels of NT-proBNP were significantly higher in NSTEMI patients (796.7pg/ml, 1860.8) than in patients with unstable angina (262.4pg/ml, 512.0) (p < 0.001). TIMI risk score range varied from zero to five points, with a median of 3.0 (IQR=2.0). Its median and IQR values were similar in both groups: 3.0 (1.0) in the unstable angina group and 2.0 (2.3) among NSTEMI patients (p = 0.89).

Ejection Fraction

Mean LVEF in the 87 patients was 60.0% (±11.0), 63.5% (±10.9) in the unstable angina group and 59.2% (±12.4%) in the NSTEMI group (p=0.10) (Table 3). LVEF > 40% was found in 86.2% of the patients, with similar number of patients in both groups (p = 0.39).

NT-proBNP correlations

There was no evidence of correlation between NT-proBNP plasma levels and TIMI risk scores (rs=0.082, p = 0.44). However, a highly significant correlation was observed between NT-proBNP, peak CK-MB (rs=0.458, p < 0.001) (Figure 1), and troponin I levels (rs=0.425, p < 0.001). There was also a correlation between NT-proBNP levels and LVEF (rs=-0.345, p = 0.002) (Figure 2).

The correlation between NT-proBNP levels, peak CK-MB (r=0.387, p < 0.001) and troponin I levels (r=0.389, p < 0.001) persisted even after adjustment for LVEF. In the multiple linear regression analysis, both troponin I levels (p=0.002) and LVEF (p = 0.017) correlated with NT-proBNP levels (r²=0.24, p < 0.001).

Discussion

The main finding of this study was the positive correlation between NT-proBNP levels and markers of myocardial necrosis in patients with NSTEMI, irrespective of LVEF. Our findings revealed a negative correlation between NT-proBNP levels and LVEF (rs=-0.345, p = 0.002), suggesting that the correlation between NT-proBNP and markers of myocardial necrosis was not caused by left ventricular dysfunction. In fact, 86.2% of our patients presented LVEF > 40%, and after a multiple linear regression analysis (r²=0.24, p < 0.001), both troponin I (p = 0.002) and ejection fraction (p = 0.017) were significantly and independently associated with NT-proBNP levels. Bazzino et al11 had already described the existence of a correlation between NT-proBNP and troponin T (r=0.23, p = 0.01), as well as a weak correlation with CK-MB (r=0.07, p < 0.001); however, those authors did not assess LVEF, a condition that, by itself, may provoke increases in natriuretic peptide levels. More recently, Palazzuoli et al14 have shown a progressive increase of BNP in stable angina, unstable angina and NSTEMI, with preservation of systolic function.

Previous studies have shown that increased levels of BNP and NT-proBNP in NSTE-ACS patients are associated with increased mortality in long-term follow-up periods after hospital discharge and a higher risk for developing heart failure.4,13,15-18. Omland et al19 conducted a study with ACS patients (STEMI, NSTEMI and unstable angina) and found that NT-proBNP is a powerful indicator of long-term mortality. The authors used echocardiography to assess LVEF in all patients; however, the association between LVEF and NT-proBNP levels was not investigated in patients with NSTE-ACS. Omland et al19 aimed to investigate the association between NT-proBNP levels and the occurrence of cardiovascular events later in life, while the investigation of this study was limited to patient’s stay at the hospital. In addition, our study excluded patients with a history of heart failure, to prevent this variable from interfering with serum NT-proBNP levels. As far as we know, this is the first study to simultaneously evaluate the correlation of NT-proBNP levels with markers of myocardial necrosis, TIMI risk score and LVEF in NSTE-ACS patients.

In our study, patient selection was based on objective diagnostic criteria, for unstable angina and for NSTEMI, and patients with non-ischemic chest pain were excluded10,19. The study focused on patients with ischemia or acute myocardial damage who presented necrosis markers above reference values, regardless of the presence of electrocardiographic abnormalities. However, the use of these strict inclusion criteria has not been the rule in previous study4,5,3,21,22. In the present study, 41.7% of the patients presented electrocardiographic ischemic changes indicative of unstable coronary disease23. This incidence is lower than in other studies, which may be explained by the fact that, as opposed to many other authors,
electrocardiographic abnormalities were not inclusion criteria in this study, in accordance with international guidelines.\(^4,10,22,23\)

In all our patients, the time elapsed between onset of ischemic symptoms and NT-proBNP assessment was shorter than 72 hours; the exact interval, however, has not been assessed. The lack of a precise time is also present in many other studies, which may represent a further limitation for the comparison of results, considering the time-dependent changes that occur in natriuretic peptide levels in NSTE-ACS patients.\(^4,7,13,17,18\)

Risk stratification is essential in managing ACS and the TIMI risk score is a valuable tool in NSTE-ACS.\(^11\) In our study, TIMI risk score did not correlate with plasma NT-proBNP levels (rs=0.082, p = 0.448). Bazzino et al\(^13\) found that NT-proBNP had a more significant prognostic value than TIMI risk score and the ACC/AHA classification in predicting the risk of cardiovascular events in patients with NSTE-ACS. However, they did not report any association between NT-proBNP and TIMI risk score, which suggests that this study is the first to note the absence of such a correlation.

In fact, our findings suggest that NT-proBNP and TIMI risk score reflect distinct aspects of NSTE-ACS. TIMI risk score is classically used in ACS as a risk marker for combined events

<table>
<thead>
<tr>
<th>Table 1 - Characteristics of 87 patients with non-ST-segment elevation acute coronary syndrome according to the diagnosis</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>General features</td>
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<tr>
<td>Age, mean (Standard deviation)</td>
</tr>
<tr>
<td>Male, n (%)</td>
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<tr>
<td>Coming from hospital emergency, n(%)</td>
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<tr>
<td>Risk factors, n (%)</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Family history for CAD</td>
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<tr>
<td>Clinical history, n (%)</td>
</tr>
<tr>
<td>Stable angina</td>
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<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>Previous CABG</td>
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<tr>
<td>Previous PCI</td>
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<tr>
<td>Peripheral arterial disease</td>
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<tr>
<td>Medication upon admission, n (%)</td>
</tr>
<tr>
<td>AAS</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>Beta-blocker</td>
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<tr>
<td>Statins</td>
</tr>
<tr>
<td>Hospital and ICU length of stay, median (IQI)</td>
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<tr>
<td>Hospital length of stay (days)</td>
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<tr>
<td>ICU length of stay (days)</td>
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</table>

NSTEMI - non-ST-segment elevation myocardial infarction, CAD – coronary artery disease, MI – myocardial infarction, CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, IQI - interquartile interval; ICU - Intensive care unit; AAS - Acetylsalicylic acid.
of coronary artery bypass grafting, myocardial infarction and death in 30 days, while NT-proBNP may be related to ischemia only during the in-hospital period.

The demonstration of a significant increase in plasma NT-proBNP levels regardless of left ventricular dysfunction in NSTE-ACS patients has important pathophysiological and clinical consequences. In experimental models with rats, the induction of myocardial hypoxia has been shown to stimulate the production of atrial and brain natriuretic peptides, as well as the rapid induction of ventricular BNP\textsuperscript{27,28}. Studies in patients submitted to percutaneous coronary interventions showed that a short-duration increase in natriuretic peptides correlated with the size of the ischemic area\textsuperscript{29,30}. Furthermore, a positive association was also observed between BNP gene expression in ventricular biopsies and plasma BNP levels in patients submitted to coronary artery bypass grafting\textsuperscript{31}. Hence, both reversible myocardial ischemia and myocardial necrosis may provoke increases in the levels of type B natriuretic peptides. More recently, it was suggested that increased BNP level can identify inducible ischemia as detected by standard noninvasive stress tests in patients with documented or suspected coronary artery disease\textsuperscript{32}. This study adds information to the findings of these studies by showing that, in NSTE-ACS patients, increased NT-proBNP levels are at least partly related to the degree of ischemic myocardial damage, which can have prognostic importance\textsuperscript{33}.

Some limitations of this study should be stressed. The studied sample is relatively small and our results have to be confirmed in larger studies. Furthermore, blood samples were collected and the echocardiogram was performed any time between the admission and 72 hours after the admission.

<table>
<thead>
<tr>
<th>ECG abnormalities, n (%)</th>
<th>UA (n = 37)</th>
<th>NSTEMI (n = 50)</th>
</tr>
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<tbody>
<tr>
<td>Absence of ischemic alterations</td>
<td>25 (67.6)</td>
<td>24 (48.0)</td>
</tr>
<tr>
<td>Transitory ST-segment elevation</td>
<td>2 (5.4)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>1 (2.7)</td>
<td>7 (14.0)</td>
</tr>
<tr>
<td>T waves abnormalities</td>
<td>9 (24.3)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>0 (0.0)</td>
<td>3 (6.0)</td>
</tr>
</tbody>
</table>

\( p = 0.08 \) by 2 x K test; NSTEMI - non-ST-segment elevation myocardial infarction; UA - Unstable angina.
beginning of the symptoms. Since both ventricular function indexes and NT-proBNP levels oscillate dynamically during the ACS, this relatively imprecise time window could be a cause of variability of the results. However, this same time window has been used in other studies4,17.

From a clinical point of view, our findings suggest that natriuretic peptide concentration in patients with NSTE-ACS can bring more relevant information than other biological markers (troponin I, CK-MB) because of their potential to better define the amount of injured myocardium. New imaging methods can define more accurately the area and location of ischemia or myocardial necrosis in the acute phase of NSTE-ACS. Studies using these methods should be done, so that the size of the ischemic/necrotic area can be analyzed in correlation with BNP and NT-proBNP levels.

**Conclusion**

In patients with NSTE-ACS, NT-proBNP correlated not only with LVEF, but also with CK-MB and troponin I levels. Increased levels of NT-proBNP in patients with

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**Table 3 - Tests during hospital stay in 87 patients with non-ST-segment elevation acute coronary syndrome**

<table>
<thead>
<tr>
<th></th>
<th>UA (n = 37)</th>
<th>NSTEMI (n = 52)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.5 (1.6)</td>
<td>13.3 (1.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.90 (0.27)</td>
<td>1.00 (0.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>183.3 (42.1)</td>
<td>203.4 (44.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>40.1 (11.7)</td>
<td>36.8 (11.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>107.5 (34.9)</td>
<td>131.5 (37.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>152.5 (90.0)</td>
<td>132.0 (108.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>CK-MB peak, UI</td>
<td>5.0 (2.0)</td>
<td>24.0 (27.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>262.4 (512.0)</td>
<td>796.7 (1860.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.5% (10.9)</td>
<td>59.2% (12.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>TIMI risk score</td>
<td>3.0 (1.0)</td>
<td>2.0 (2.3)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation), except * expressed by median (interquartile range); NSTEMI - non-ST-segment elevation myocardial infarction; UA - Unstable angina.

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**Figure 2 - Correlation between the NT-proBNP logarithm and the ejection fraction in 87 patients with non-ST-segment elevation acute coronary syndrome (rs = -0.345, p = 0.002).**
NSTE-ACS are not related exclusively to low LVEF, but can also be caused by the presence of myocardial ischemia and necrosis.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**References**


**Sources of Funding**

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**Study Association**

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