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Predictive Value of High Sensitivity-Troponin T for Systolic Dysfunction and Infarct Size (6 months) after ST-Elevation Myocardial Infarction

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Running title: High sensitivity-Troponin T predicts long-term systolic dysfunction

Key words: STEMI, Troponin, Infarct size, Ejection fraction

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Abstract
The association of markers of myocardial injury and dysfunction with infarct size (IS) and ejection fraction (EF) are well documented. However, limited data is available on the newer high sensitivity troponin assays and comparison with morphological and functional assessment with cardiac magnetic resonance imaging (CMR). We aimed to examine the associations of high sensitivity cardiac Troponin-T (hs-cTnT), Creatine Kinase MB iso-enzyme (CKMB) and N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) to infarct size (IS) and ejection fraction (EF) at 6 months. Blood samples from 119 ST-segment elevation myocardial infarction (STEMI) patients from the Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI) trial were collected at baseline, 6hrs, 24hrs and 48hrs after admission. CMR was performed at 4±2 days and 6 months. The association of biomarker levels to IS and EF were tested with Pearson’s correlation coefficients and linear regression models with bootstrap resampling. The correlation coefficient of biomarker to IS was (CKMB: r=0.71); (NT-proBNP: r=0.55); (hs-cTnT: r=0.80) and for EF and (CKMB: r=0.57); (NT-proBNP: r=0.48); (peak hs-cTnT: r=0.68). IS and EF at 4±2 days had the strongest correlations with IS and EF at 6 months respectively (IS: r=0.84) and (EF: r=0.74). ROC of peak hs-cTnT for predicting EF≤40% at 6 months was 0.87 compared to 0.75 for early IS. Early EF was a negative predictor of late EF<40%, 1-AUC=0.93. In conclusion, high-sensitivity Troponin T is a rapid, cheap, generally available tool for accurate prediction of systolic dysfunction in patients 6 months after first-time STEMI

Key Words: STEMI, Troponin, Infarct size, Ejection fraction
Introduction

High-sensitivity troponin assays are currently the preferred biomarker assays for the diagnosis of myocardial infarction\textsuperscript{1,2}. Biomarkers in myocardial infarction are useful for the diagnosis of myocardial infarction and for estimation of the extent of myocardial damage. The amount of biomarker leaking to plasma directly relates to the size of infarcted myocardium. The size of the infarct is a strong predictive measure of short- and long-term outcome after ST-elevation Myocardial Infarction (STEMI) as well as ejection fraction and heart failure development.\textsuperscript{3,4} Early information regarding the risk for long-term heart failure development is important to guide medical treatment and need for implantable cardioverter defibrillator. Although large studies using SPECT as method for infarct size quantification have shown strong correlation between troponin and CKMB to infarct size and ejection fraction, the sensitivity of SPECT imaging for smaller infarctions is inferior to CMR.\textsuperscript{5-7} Studies utilizing CMR on the other hand have either been limited in size or utilized older troponin assays,\textsuperscript{8-15} but have consistently observed strong correlation between biomarkers and infarct size. To date, two studies have assessed the relationship of hs-cTnT with infarct size and ejection fraction\textsuperscript{16,17}. These studies not only need to be confirmed in external cohorts but moreover, the biomarkers need to be compared to the golden standard reference for infarct size assessment. No study has compared the use of plasma hs-cTnT, Creatine Kinase MB iso-enzyme (CKMB) and N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) in myocardial infarction to early CMR for assessment of infarct size and ejection fraction with longer follow-up. The aims of this study was therefore to assess the relation of the most commonly used biomarkers (hs-cTnT, CKMB and NT-proBNP) in reperfused STEMI to long-term infarct size
and ejection fraction and compare them with infarct size with late gadolinium enhancement (LGE) CMR at 4±2 days.

**Methods**

All patients from the Randomized Controlled Study of the Use of Central Venous Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI trial) were included in this post-hoc analysis. The study design for the CHILL-MI trial has been published previously, but in brief included patients with STEMI that underwent percutaneous coronary intervention (PCI) between July 2011 and March 2013 from 9 sites in 4 countries. Participants were randomized to hypothermia induced by rapid infusion of cold saline and endovascular cooling or standard care. Patients with cardiac arrest, previous myocardial infarction (MI), previous PCI or coronary artery bypass grafting (CABG), known congestive heart failure, end-stage kidney disease or hepatic failure, recent stroke, coagulopathy, pregnancy, or Killip class II to IV at presentation were excluded. A total of 120 patients were randomized of whom 117 underwent PCI. Blood samples were available for 119 patients. The Ethics Committee of Lund University approved the study and all participants provided informed consent, in agreement with the declaration of Helsinki. The primary analyses were the correlation and linear associations of hs-cTnT, CKMB and NTproBNP to long-term infarct size (% of LVM) and ejection fraction to compare them with early infarct size and ejection fraction at 4±2 days. An explorative, pre-specified subgroup analysis stratified on culprit vessel was also conducted.

Blood samples were collected at baseline before start of hypothermia and PCI (0hrs), 6hrs, 12hrs, 24hrs and 48hrs post PCI by peripheral venous puncture and
heparinized plasma sample were analysed (Elecsys Troponin T high sensitivity assay, Roche Diagnostics; Elecsys CKMB assay, Roche Diagnostics; Elecsys NT-proBNP, Roche Diagnostics). All analyses were performed in a core lab at Uppsala Clinical Research centre and were stored locally at -80° until shipment on dry ice with courier.

A total of 101 patients underwent CMR at day 4±2 days and 86 at 6 months after STEMI, the reasons for dropout of CMR are presented elsewhere. The CMR examination was performed in the supine position. After initial scout images to locate the heart and the standard imaging planes, 0.2 mmol per kilogram of body weight of an extracellular gadolinium-based contrast agent were administered. For visualization of the myocardium at risk (MaR) and evaluation of LVEF, early contrast-enhanced steady state free precession cine images were obtained approximately 5 minutes after contrast injection. For infarct visualisation, LGE images were acquired 15-20 minutes after administration of the contrast agent. Cine and LGE images were acquired in the short-axis view, from base to apex, and in the three standard long-axis views (two-chamber, four-chamber and left ventricular outflow tract views), during breath-hold image sequence. The analysis of ventricular dimensions, MaR and infarct size was performed by a core lab (Imacor AB, Lund, Sweden) using a post-processing software (Segment, v.1.9 R3084; http://segment.heiberg.se). Infarct size was expressed as a percentage of the left ventricular myocardium (IS/LVM) and gram. Observers blinded to all other data performed the assessment of infarct size and ejection fraction. Infarct size was available in 97 of 101 at 4±2 days and 82 of 86 6 months whereas ejection fraction were available for all individuals that underwent CMR.

Statistics
Continuous variables are expressed as means with standard deviations when normally distributed and as medians with interquartile range (IQR) when not normally distributed. Normality of distributions was assessed from visual inspection of histograms. The primary endpoints were infarct size (% of LVM) and ejection fraction (%) at 6 months. Linear regression models with bootstrap resampling with 10,000 replications were implemented as the primary analysis model. The residuals were checked visually as well as tests for homogeneity of variance. The coefficient of determination ($R^2$) was determined from the linear regression model and Pearson’s coefficient of correlation was calculated with bootstrap resampling with 10,000 replications. The area under the Receiver Operating Characteristics (ROC) curve was used to evaluate predictive ability (C-index). To simplify interpretation of negative associations in C-indices, they will be considered as 1-AUC. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using STATA version 14.1 for Macintosh, StataCorp, Texas.

**Results**

The mean age and standard deviation (SD) at admission was 57.5±10.0 years and 98 patients (82%) were males. The right coronary artery (RCA) was the culprit artery in 56 (47.1%) and 50 (42%) had the left anterior descending artery (LAD) as culprit artery. A total of 91.6% had TIMI flow grade 3 after PCI. All patient characteristics together with mean biomarker values and CMR measures are presented in Table 1. Time concentration curve for biomarkers are presented in Figure 1. Mean ejection fraction (%) at 4±2 days was 48±9 and increased to 51±10 at 6 months, Table 1.
Scatterplots illustrating the relation of each biomarker to infarct size and ejection fraction at 6 months with coefficient of determination (R²) and root mean square error (RMSE) are shown in Figure 2. The AUC of hs-cTnT had the highest R² with 64% of total variation in final infarct size being explained by the linear relationship to troponin (r=0.80). Whereas peak hs-cTnT achieved a slightly lower R² for infarct size, AUC and peak hs-cTnT performed equally well with regard to ejection fraction, Figure 2. A stronger correlation was observed in the subgroup analysis of RCA infarctions for infarct size and similarly for LAD infarctions and ejection fraction (Figure 3). For early infarct size, the correlation coefficient for AUC of hs-cTnT was r=0.72 (R²=0.52); CKMB (AUC) r=0.55 (R²=0.30); CKMB (peak) r=0.60 (R²=0.36) and NT-proBNP r=0.63 (R²= 0.40). The correlations of early CMR to long-term infarct size and ejection fraction are presented in Figure 4. Infarct size measured at 4±2 days had the strongest correlation with long-term infarct size and ejection fraction at 4±2 days had the strongest correlation with ejection fraction at 6 months. One standard deviation increase in AUC of Hs-cTnT was associated with a 5.6% increase in infarct size (% of LVM) (p<0.001) and a reduction of 7.3% in EF at 6 months (p<0.001). The impact of remaining biomarkers on infarct size and ejection fraction is presented in Table 2.

Sixteen patients had an ejection fraction <40% at 6 months. The area under the receiver operator characteristic (ROC) curve of cumulative hs-cTnT (0-48hrs) for prediction of long-term ejection fraction ≤40% was 0.856 and slightly higher for peak hs-cTnT, AUC=0.866 with no significant difference between curves, p=0.75. A test of comparison of ROC for peak hs-cTnT and ROC for infarct size (% of LVM) at 4±2 days was statistically significant, p=0.04. The ROC for peak CKMB was 0.828 and 0.810 for NT-proBNP, as shown in Figure 5. The optimal cut-off to rule out ejection
fraction <40% 6 months after STEMI for peak hs-cTnT was a value <3500ng/L. Out of all true negative individuals (31%) with this cut-off, no individual testing with a negative test had an ejection fraction<40% at 6 months. Accordingly, a peak hs-cTnT of >13000ng/L identified all true positive individuals (31%) and all individuals with a positive test had an ejection fraction<40% at 6 months, Figure 6.

Discussion

In the present study, we confirmed the correlation of hs-cTnT, CKMB and NTproBNP to long-term infarct size and ejection fraction assessed by CMR in patients with first-time STEMI undergoing primary PCI. Furthermore, we compared them to the performance of early morphological and functional assessment by CMR at 4±2 days. Our main finding is that the correlation of hs-cTnT to long-term infarct size and ejection fraction was overall similar to early CMR assessment of infarct size and ejection fraction. CMR is an expensive, time consuming, laborintense diagnostic modality, which requires proper patient compliance during investigation for adequate imaging quality. In contrast, high-sensitivity Troponin T, is rapid and generally available in clinical practice, and could accurately predict long-term systolic dysfunction and infarct size in revascularized first-time STEMI patients.

Troponin is known to be a strong surrogate marker for the extent of myocardial infarct size however, only one study of hs-cTnT with long-term CMR measures is available up to date. Moreover, no study has investigated these associations and compared them to early CMR. In a prospective study on 60 low-risk STEMI patients undergoing PCI, Reinstadler et al investigated the correlation of hs-cTnT, CKMB and NTproBNP to infarct size and ejection fraction assessed by CMR.
at baseline and 1 year after admission. In line with previous studies with older troponin assays, hs-cTnT was strongly correlated with infarct size and ejection fraction and although the cut-off used for left ventricular dysfunction was <55%, ROC results were comparable with peak hs-cTnT being the strongest predictor for LV dysfunction. The observed correlation coefficients were slightly lower than in our study although similar mean infarct size and peak hs-cTnT levels were observed between both cohorts. In a study of 201 first time STEMI patients, peak, 48hrs and 72hrs hs-cTnT levels were strongly correlated with infarct size and ejection fraction at median 4 days after admission. In accordance with our results, peak hs-cTnT resulted in a ROC value of 0.84 for ejection fraction <40%. However no measurements were assessed 6hrs and 12hrs after admission potentially missing the true peak.

Although cardiac troponins exert the highest cardiac specificity of any biomarker known to date, troponins are not specific to the aetiology of myocardial infarction. It is therefore unclear if the release of cardiac troponin is solely from the infarcted myocardium or whether ischemic and failing myocardium constitutes a source of troponin leakage. Although CKMB is less cardiac specific than troponin, there is evidence that release of CKMB reflects an irreversible myocardial damage and thus represent infarcted myocardium rather than ischemia. The lower correlation of CKMB with early infarct size as compared to final infarct size in our study further supports this evidence. The discrepancy between infarct size at 4±2 days and 6 months may be explained by an overestimation of early infarct size due to oedema, Table 1 and Figure 4. In our study, mean ejection fraction increased with 3.4% percentage units in ejection fraction, equivalent to a 7% increase, most likely due to resolve of myocardial stunning. This increase in ejection fraction is in line with previous reported studies.
Interestingly, final infarct size was not superior to area under the curve or peak hs-cTnT in predicting long-term ejection fraction <40% thus indicating that although there is a high degree of correlation, infarct size alone does not explain all the variance in ejection fraction, Figure 3 and 4. Peak hs-cTnT seems to be an excellent tool for risk stratification and although the intermediate cut-off for progression to heart failure may provide excellent specificity, sensitivity and negative predictive value (NPV) as well as great positive predictive value (PPV), we advocate a multi cut-off approach for “rule in/rule out” of long-term heart failure, Figure 5. Whereas the CMR is gold standard for assessment of infarct size and ejection fraction, our results confirm and further strengthen previous studies with hs-cTnT as an excellent surrogate biomarker. However, this requires that laboratories assess the entire troponin spectrum and not cap the results at an upper range of 9999ng/L as is practice in many laboratories today.

In conclusion, high-sensitivity Troponin T could be a feasible tool guiding the need for more intensive imaging, medical or mechanical device therapies in patients after PCI-reperfused first-time ST-elevation myocardial infarction. Further studies validating these findings are warranted. However, a number of issues need to be addressed. First, it is very reasonable to extrapolate these correlations to hs-cTnI assays however, the lack of standardization remains a problem. Considering the observed correlation variability in the different culprit lesion models, a culprit lesion-stratified model might be considered. The optimal measure of hs-cTnT needs to be established (single-point, peak or AUC) as different studies have shown varying results.6,8,9,16

The strength of our study lies in utilizing a prospective, international multi-centre patient cohort from a well-known clinical trial. However, it is important to
acknowledge that our results are constricted to a relatively young patient population, without previous myocardial infarctions, PCI, CABG or heart failure. In the CHILL-MI trial, no effect of hypothermia was observed on the level of hs-cTnT and treatment arm was therefore not adjusted for in the multivariable analysis\textsuperscript{18}. This could however have affected the results. Due to the limited sample size, no internal validation on a test sample or comparison between correlation coefficients was done. The fact that patients underwent 2 consecutive CMRs allowed for unique comparison of the most commonly used biomarkers in cardiovascular setting to early morphological and functional assessment.

**Funding**

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**Conflicts of interest:**

B Lindahl has received consulting fees from Roche Diagnostics, bioMérieux Clinical Diagnostics, Philips Healthcare, ThermoFischer and Fiomi Diagnostics; and has received a research grant from bioMérieux Clinical Diagnostics and Fiomi Diagnostics, H Arheden, P Clemmensen, T Engstrøm, D Erlinge, M Holzer, S James, U Jensen, S Koul, I Lang, B Metzler, MA Mohammad, M Noc, JG Smith, and have nothing to declare.
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Figure 1. Time-concentration curve for hs-cTnT and CKMB.

Time-concentration curve for hs-cTnT and CKMB demonstrating their release profile after PCI. Peak occurs at 12hrs for hs-cTnT and 6hrs for CKMB.

CKMB= Creatine Kinase MB iso-enzyme; hs-cTnT=high sensitivity-cardiac Troponin T.

Figure 2. Scatterplot for peak and AUC of CKMB, NTproBNP at 4±2 days and peak and AUC of hs-cTnT.

Correlation between AUC of CKMB, peak CKMB, NTproBNP at 4±2 days, AUC of hs-cTnT and peak hs-cTnT to CMR assessed infarct size and left ventricular ejection fraction at 6 month.

Figure 3. Scatterplot for AUC of hs-cTnT stratified by culprit vessel.

Correlation of cumulative release of hs-cTnT with infarct size and ejection fraction at 6 months stratified according to vascular territory.

LAD=Left Anterior Descending Artery; LCx=Left Circumflex Artery; RCA=Right Coronary Artery.

Figure 4. Scatterplot for early and long-term CMR.

Correlation between early infarct size and ejection fraction to infarct size and ejection fraction at 6 months. LVM= Left Ventricular Mass.
Figure 5. ROC for AUC and peak hs-cTnT, early infarct size and ejection fraction for prediction of ejection fraction <40% at 6 months.

Early ejection fraction predicted heart failure defined as ejection fraction <40% best followed by peak hs-cTnT. Significant difference observed between ROC for peak hs-cTnT and infarct size, p=0.04. Ejection fraction was a negative predictor of heart failure resulting in a ROC<0.5.

Figure 6. Optimal peak hs-cTnT cut-offs for rule in and rule out ejection fraction <40% at 6 months.

Proposed cut-offs for peak hs-cTnT for rule in and rule out of ejection fraction <40% at 6 months with sensitivity, specificity, negative predictive value and positive predictive value.

NPV=Negative Predictive Value; PPV=Positive Predictive Value.
Table 1. Clinical, angiographic and cardiac magnetic resonance imaging data.

<table>
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<th>Variable</th>
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<th>Cardiac Magnetic Resonance Imaging - 4±2 days</th>
<th>Cardiac Magnetic Resonance Imaging - 6 months</th>
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<td>Age (Years)</td>
<td>57.5±10.0</td>
<td>57.7±10.4</td>
<td>58.4±10.1</td>
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<tr>
<td>Male</td>
<td>98 (82.3%)</td>
<td>85 (84.2%)</td>
<td>75 (87.2%)</td>
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<tr>
<td>Female</td>
<td>21 (17.7%)</td>
<td>16 (15.8%)</td>
<td>11 (12.8%)</td>
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<tr>
<td>Body mass index (Kg/m²)</td>
<td>27.6±4.1</td>
<td>27.4±3.8</td>
<td>27.3±3.7</td>
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<tr>
<td>Smoker</td>
<td>51 (42.9%)</td>
<td>42 (41.6%)</td>
<td>35 (40.7%)</td>
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<tr>
<td>Ex-smoker</td>
<td>30 (25.2%)</td>
<td>26 (25.7%)</td>
<td>22 (25.6%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>11 (9.2%)</td>
<td>9 (8.9%)</td>
<td>8 (9.3%)</td>
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</tbody>
</table>
Table 1. Clinical, angiographic and cardiac magnetic resonance imaging data.

Clinical, angiographic and cardiac magnetic resonance imaging (CMR) data for all patients, those who underwent CMR at 4±2 days and 6 months.

Table 2. Linear regression model results.

<table>
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<td>Infarct size (% of LVM)</td>
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<tr>
<td>AUC high sensitivity-cardiac Troponin T</td>
<td>5.63 (4.58-6.67) p&lt;0.001</td>
<td>5.62 (4.54-6.70) p&lt;0.001</td>
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<tr>
<td>Peak high sensitivity-cardiac Troponin T</td>
<td>5.38 (4.28-6.48) p&lt;0.001</td>
<td>5.40 (4.27-6.54) p&lt;0.001</td>
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<tr>
<td>AUC Creatine Kinase MB iso-enzyme</td>
<td>4.43 (3.28-5.58) p&lt;0.001</td>
<td>4.54 (3.36-5.73) p&lt;0.001</td>
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<tr>
<td>Peak Creatine Kinase MB iso-enzyme</td>
<td>4.33 (2.90-5.78) p&lt;0.001</td>
<td>4.53 (3.02-6.04) p&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>4.77 (3.05-6.48) p&lt;0.001</td>
<td>5.52 (3.82-7.23) p&lt;0.001</td>
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</table>
Results are interpreted as percentage increase in infarct size (% of LVM) or decrease in ejection fraction with one increase in standard deviation of each biomarker measure. NT-proBNP was measured at 4±2 days. Adjusted models were adjusted for: sex, body mass index and age.

AUC=Area Under Curve; LVM=Left Ventricular Mass.

<table>
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<th>Coef (95% CI)</th>
<th>P-value</th>
<th>Coef (95% CI)</th>
<th>P-value</th>
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<tr>
<td>AUC high sensitivity- cardiac Troponin T</td>
<td>-7.27 (-8.85- -5.70)</td>
<td>p&lt;0.001</td>
<td>-7.32 (-8.88- -5.75)</td>
<td>p&lt;0.001</td>
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<tr>
<td>Peak high sensitivity- cardiac Troponin T</td>
<td>-7.12 (-8.85- -5.39)</td>
<td>p&lt;0.001</td>
<td>-7.12 (-8.87- -5.38)</td>
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<td>AUC Creatine Kinase MB iso-enzyme</td>
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<td>p&lt;0.001</td>
<td>-5.61 (7.32- -3.90)</td>
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<td>p&lt;0.001</td>
<td>-5.89 (7.46- -4.32)</td>
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<tr>
<td>NT-proBNP</td>
<td>-6.40 (-8.78- -4.01)</td>
<td>p&lt;0.001</td>
<td>-7.11 (-9.61- -4.61)</td>
<td>p&lt;0.001</td>
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