The influence of severe mitral regurgitation on major adverse cardiac and cerebrovascular events after myocardial infarction in 1-year follow-up: Data from the PL-ACS registry

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ABSTRACT

Background: Mitral regurgitation (MR) is frequently observed in patients with myocardial infarction (MI). However, the incidence of severe MR in the contemporary population is unknown.

Aims: The study evaluates the prevalence and prognostic impact of severe MR in the contemporary population of patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

Methods: The study group consisted of 8062 patients enrolled in the Polish Registry of Acute Coronary Syndromes (PL-ACS) in the years 2017–2019. Only the patients with full echocardiography performed during the index hospitalization were eligible. The primary composite outcome was 12-month major adverse cardiac and cerebrovascular events (MACCE) (death, non-fatal myocardial infarction, stroke, and heart failure [HF] hospitalization) compared between patients with and without severe MR.

Results: 5561 NSTEMI patients and 2501 STEMI patients were enrolled in the study. Severe MR occurred in 66 (1.19%) NSTEMI patients and 30 (1.19%) STEMI patients. Multivariable regression models demonstrated that severe MR is an independent risk factor for all-cause death in 12-month follow-up (odds ratio [OR], 1.839; 95% confidence interval [CI], 1.012–3.343; P = 0.046) in all MI patients. Patients with NSTEMI and severe MR had higher mortality (22.7% vs. 7.1%), HF rehospitalization rate (39.4% vs. 12.9%), and MACCE occurrence (54.5% vs. 29.3%). Severe MR was associated with higher mortality (20% vs. 6%) and higher HF rehospitalization rate (30% vs. 9.8%), stroke (10% vs. 0.8%), and MACCE rates (50% vs. 23.1%) in STEMI patients.

Conclusions: Severe MR is associated with higher mortality and MACCE occurrence in patients with MI in 12-month follow-up. Severe MR is an independent risk factor for all-cause death.

Key words: mitral regurgitation, mortality, myocardial infarction
WHAT’S NEW?
The present study showed that in patients with acute myocardial infarction (non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction) severe mitral regurgitation is strongly associated with increased mortality and occurrence of major adverse cardiac and cerebrovascular events in 12-month follow-up. Moreover, it is an independent risk factor for all-cause death. Taking into consideration these results, early echocardiographic assessment of mitral regurgitation becomes a crucial element in determining the prognosis of patients after myocardial infarction, which enables appropriate treatment implementation.

INTRODUCTION
Cardiovascular diseases, especially ischemic heart disease, remain among the most prevalent causes of mortality and morbidity responsible for 19%–20% of deaths in Europe [1]. Valvular heart disease (VHD) may complicate clinical course of acute coronary syndromes (ACS) [2, 3]. Mitral regurgitation (MR) of any severity is frequently observed in patients with acute myocardial infarction (MI) [3–23], affecting up to 50% of patients [13, 17]. In the era before widespread use of primary percutaneous coronary interventions (PCI) and longer delays from symptom onset to treatment, MR was reported as a poor prognostic factor [4–6, 8, 10–19], associated with an increase in mortality rates [4–6, 8, 12–19]. Most studies assessed this association in the mild and moderate stage of MR [4, 10, 12, 13, 16] in both the acute [11, 16] and chronic [4–6, 8, 10–17] phase after MI. It is less clear how severe MR affects the outcomes in the contemporary population of non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) patients treated invasively in the all-comer nationwide registry.

The present study aimed to evaluate specifically the prevalence and prognostic implication of severe MR in patients with acute MI in relation to in-hospital and 12-month outcomes. In this registry, we assessed both STEMI and NSTEMI patients. The study group included patients enrolled in the nationwide Polish Registry of Acute Coronary Syndromes (PL-ACS).

METHODS

Registry design
We used data from the PL-ACS registry database which has been an ongoing nationwide registry since 2003. It collects specific data on clinical characteristics, in-hospital management, and discharge treatment of all patients with ACS. The registry was established as a cooperative initiative of the Silesian Center for Heart Diseases in Zabrze and the Polish Ministry of Health. Design, methods, and logistic aspects of the PL-ACS were described previously [24, 25]. According to the protocol, all admitted patients with the initial diagnosis of ACS were evaluated for eligibility to enter the registry, and they were not enrolled until ACS had been confirmed. Patient data were gathered and analyzed by experienced physicians and entered directly in an appropriate web-based form.

Data collection and study group profile
Before the beginning of 2021, the PL-ACS included almost 783 000 patients. To obtain a 12-month follow-up, all patients discharged before the end of 2019 were considered. Then, the patients with the diagnosis of unstable angina were excluded. Since follow-up data were available only from the regional Silesian branch of the National Health Fund and only for the years 2017–2019, 466 642 patients were excluded. Twelve different hospitals from the Silesia region provided follow-up data. Only one additional patient was excluded due to the missing data in the ejection fraction (EF) measurements. The echocardiographic evaluation was performed during the index hospitalization. Only the patients with a detailed echocardiographic description of valvular disease were included. After that, the patients with severe aortic stenosis, severe aortic regurgitation, or severe mitral stenosis, and those who did not survive index hospitalization were excluded. After excluding patients in whom coronary angiography was not performed, the final study group consisted of 8062 individuals (Figure 1).

Endpoints and definitions
The major adverse cardiac and cerebrovascular events (MACCE), assessed within the 12-month follow-up, were defined as all-cause death, non-fatal MI, stroke, and rehospitalization for heart failure (HF). Non-fatal MI was defined per the European Society of Cardiology (ESC) MI criteria [26]. Stroke was defined as an acute neurological deficit that lasted over 24 hours and was confirmed by a neurologist. The study involved only the patients with a confirmed diagnosis of STEMI or NSTEMI, meeting the ESC MI criteria [26]. The data collection period was from 2017 to 2019. The definition of severe MR during that time did not change despite the publication of new ESC guidelines for the management of valvular heart disease at the end of 2017 [27, 28]. The comorbidity definitions which changed during that time were updated due to the guidelines issued by European scientific societies.

Study hypothesis and objectives
In this study, it was hypothesized that the presence of severe MR significantly influences prognosis of MI patients. The study group was divided into two subgroups...
depending on whether patients were admitted with STEMI or NSTEMI. Each group was then further split into two subgroups: with or without severe MR (Figure 1). We compared the differences in terms of demographic data, clinical characteristics, treatment strategy, drugs prescribed on discharge, in-hospital and 12-month outcomes including the number of MACCEs.

**Statistical analysis**

Baseline demographic and clinical characteristics, angiographic findings, in-hospital adverse events, drugs on discharge, and events in the 12-month follow-up were compared depending on the diagnosis of severe MR and type of MI. Continuous variables were summarized using the arithmetic mean with standard deviation (SD) for normal distribution or median with interquartile range (IQR) for non-normal distribution. Normality of distribution was verified using the Shapiro-Wilk test. Continuous variables with normal distribution were compared using Student’s t-test, whereas variables with skewed distribution were compared using the Mann-Whitney U test. Categorical variables were summarized using frequency tables. The χ² test with Yates’s modification was used for the comparison of categorical data, if applicable. Long-term survival was compared using the log-rank test, and the Kaplan-Meier model was used to present cumulative survival probability. The multivariable analyses of factors affecting 12-month mortality and MACCE occurrence were performed. Forward stepwise logistic regression with cross-validation was used. The multivariable models for 12-month mortality and MACCE occurrence included over 20 variables. Statistical significance was defined as P <0.05. All statistical analyses were performed using Statsoft Statistica software.

**RESULTS**

**Population characteristics**

As shown in Supplementary material, Figure S1, the final analysis included 8062 patients with known echocardiographic findings related to VHD. Figure 1 illustrates distribution of patients with MR depending on the diagnosis of STEMI (31%; n = 2501) or NSTEMI (69%; n = 5561). Those two subgroups were then further divided into severe MR+ and severe MR- subgroups.

In the NSTEMI subgroup, the patients with severe MR were more often previously diagnosed with coronary artery disease (CAD), HF, atrial fibrillation (AF), and chronic kidney disease, and had more often a history of coronary artery bypass graft (CABG) and pacemaker (PM) implantation. In the STEMI subgroup, the patients with severe MR were older and had a higher prevalence of AF. Table 1 shows the baseline demographic data.

With regard to concomitant VHD (Supplementary material, Table S2), moderate and severe tricuspid regurgitation (TR) was significantly more often identified in the severe MR+ subgroup in the NSTEMI subgroup. In patients with both MI types, a higher New York Heart Association (NYHA) class on discharge was typical of patients with severe MR.

For the STEMI subgroup, the patients with severe MR were more often previously diagnosed with coronary artery disease (CAD), HF, atrial fibrillation (AF), and chronic kidney disease, and had more often a history of coronary artery bypass graft (CABG) and pacemaker (PM) implantation. In the STEMI subgroup, the patients with severe MR were older and had a higher prevalence of AF. Table 1 shows the baseline demographic data.

**Abbreviations:** MR, mitral regurgitation; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

![Figure 1. Study group division](image-url)
As shown in Supplementary material, in-hospital management MR subgroups, regardless of MI type. Moderate aortic regurgitation (AR) was more frequent in patients with severe MR in the NSTEMI subgroup.

**In-hospital management**

As shown in Supplementary material, Table S3, in the NSTEMI subgroup, use of radial access was significantly lower in severe MR+ vs. severe MR-patients. Severe MR was associated with a higher number of stenoses in coronary arteries in both the STEMI and NSTEMI subgroups. There was also a significant difference in terms of distribution of coronary lesions between severe MR+ and severe MR-patients with NSTEMI. In the subgroup with NSTEMI, PCI was performed more often in the severe MR- subgroup.

During index hospitalization (Table 2), both in the STEMI and NSTEMI subgroups, patients with severe MR had pulmonary edema more often. A tendency for more frequent shock diagnosis could be seen in the severe MR+ subgroup in the NSTEMI subgroup.

Supplementary material, Table S4, presents drugs prescribed on discharge. Diuretics and aldosterone receptor antagonists (MRA) were given more frequently to patients with severe MR, in both MI-type subgroups. Furthermore, in the NSTEMI subgroup, anticoagulants were prescribed more frequently in the severe MR subgroup. At the same time, acetysalicylic acid (ASA) was given less often in the same subgroup.

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI (n = 3561)</th>
<th>STEMI (n = 2501)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe MR+ (n = 66)</td>
<td>Severe MR- (n = 3495)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>70.2 (10.5)</td>
<td>68.6 (10.5)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>20 (30.3)</td>
<td>1927 (31.5)</td>
</tr>
<tr>
<td>Hypertension, n/n (%)</td>
<td>52/59 (88.1)</td>
<td>4190 (80.5)</td>
</tr>
<tr>
<td>Hyperlipidemia, n/n (%)</td>
<td>33/58 (56.9)</td>
<td>2995 (61.5)</td>
</tr>
<tr>
<td>Active smoker, n/n (%)</td>
<td>30/44 (68.2)</td>
<td>2809 (59.9)</td>
</tr>
<tr>
<td>Diabetes, n/n (%)</td>
<td>24/59 (40.7)</td>
<td>1698 (33.1)</td>
</tr>
<tr>
<td>Obesity, n/n (%)</td>
<td>18/50 (36.0)</td>
<td>1110 (23.1)</td>
</tr>
<tr>
<td>CAD, n/n (%)</td>
<td>30/64 (46.9)</td>
<td>1323 (26.1)</td>
</tr>
<tr>
<td>MI, n/n (%)</td>
<td>28/64 (43.8)</td>
<td>1609 (31.2)</td>
</tr>
<tr>
<td>PCI, n/n (%)</td>
<td>29/64 (45.3)</td>
<td>1638 (31.8)</td>
</tr>
<tr>
<td>CABG, n/n (%)</td>
<td>15/62 (24.2)</td>
<td>514 (10.1)</td>
</tr>
<tr>
<td>HF, n/n (%)</td>
<td>23/61 (37.7)</td>
<td>610 (12.0)</td>
</tr>
<tr>
<td>AF, n/n (%)</td>
<td>24/63 (38.1)</td>
<td>796 (15.6)</td>
</tr>
<tr>
<td>Stroke, n/n (%)</td>
<td>3/61 (4.9)</td>
<td>327 (6.5)</td>
</tr>
<tr>
<td>CKD, n/n (%)</td>
<td>17/62 (27.4)</td>
<td>608 (12.0)</td>
</tr>
<tr>
<td>PAD, n/n (%)</td>
<td>10/60 (16.7)</td>
<td>561 (11.2)</td>
</tr>
<tr>
<td>COPD/asthma, n/n (%)</td>
<td>2/61 (3.3)</td>
<td>346 (6.9)</td>
</tr>
<tr>
<td>History of malignancy, n/n (%)</td>
<td>3/61 (4.9)</td>
<td>182 (3.7)</td>
</tr>
<tr>
<td>PM, n/n (%)</td>
<td>6/63 (9.5)</td>
<td>153 (3.0)</td>
</tr>
<tr>
<td>ICD, n/n (%)</td>
<td>3/63 (4.8)</td>
<td>77 (1.5)</td>
</tr>
<tr>
<td>CRT-D, n/n (%)</td>
<td>1/63 (1.6)</td>
<td>42 (0.8)</td>
</tr>
</tbody>
</table>

Obesity defined as BMI (body mass index) >30 kg/m²

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MR, mitral regurgitation; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, pacemaker; STEMI, ST-segment elevation myocardial infarction

### Follow-up

Twelve-month follow-up is presented in Table 2. The median follow-up was 19.5 (12.9–27.1) months. In the subgroup of patients with NSTEMI, individuals with severe MR had higher mortality, were more often rehospitalized for HF, and had higher MACCE occurrence. Furthermore, they had more often implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) implantation. Similarly in the STEMI subgroup, patients with severe MR had a higher mortality rate, were more often rehospitalized for HF, and had more frequently CRT implanted. Additionally, in this subgroup, stroke occurred significantly more often. The rate of composite MACCE was also significantly higher. The Kaplan-Meier estimators (Figures 2–5, Supplementary material, Figures S2–S4) present the distribution of events over time during the follow-up period.

Analysis of multivariable models for 12-month mortality (Table 3) and MACCE (Supplementary material, Table S5) occurrence showed that in the population after MI, severe MR is an independent risk factor for all-cause death in 12-month follow-up. At the same time, severe MR is not an independent risk factor for MACCE occurrence during 12-month follow-up.

### DISCUSSION

The present study shows that severe MR is infrequent in the contemporary population of patients with acute MI.
Table 2. Events during hospitalization and 12-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI (n = 3561)</th>
<th>STEMI (n = 2501)</th>
<th>P-value</th>
<th>NSTEMI (n = 3561)</th>
<th>STEMI (n = 2501)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events during hospitalization</strong></td>
<td></td>
<td></td>
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<tr>
<td>Shock, n (%)</td>
<td>2 (3.0)</td>
<td>31 (0.6)</td>
<td>0.08</td>
<td>2 (6.7)</td>
<td>49 (2.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Pulmonary edema, n (%)</td>
<td>3 (4.6)</td>
<td>45 (0.8)</td>
<td>0.09</td>
<td>2 (6.7)</td>
<td>21 (0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>1 (1.5)</td>
<td>22 (0.4)</td>
<td>0.57</td>
<td>0 (0)</td>
<td>9 (0.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>1 (1.5)</td>
<td>11 (0.2)</td>
<td>0.16</td>
<td>0 (0)</td>
<td>6 (0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>2 (3.0)</td>
<td>78 (1.4)</td>
<td>0.74</td>
<td>0 (0)</td>
<td>44 (1.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>SCA in hospital, n (%)</td>
<td>1 (1.5)</td>
<td>30 (0.5)</td>
<td>0.77</td>
<td>1 (3.3)</td>
<td>39 (1.6)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>12-months follow-up events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>15 (22.7)</td>
<td>388 (7.1)</td>
<td>&lt;0.001</td>
<td>6 (20.0)</td>
<td>148 (6.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>9 (13.6)</td>
<td>819 (14.9)</td>
<td>0.99</td>
<td>3 (10.0)</td>
<td>273 (11.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hospitalization for HF, n (%)</td>
<td>26 (39.4)</td>
<td>709 (12.9)</td>
<td>&lt;0.001</td>
<td>9 (30.0)</td>
<td>242 (9.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>1 (1.5)</td>
<td>98 (1.8)</td>
<td>0.10</td>
<td>3 (10.0)</td>
<td>19 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MACCE, n (%)</td>
<td>36 (54.5)</td>
<td>1612 (29.3)</td>
<td>&lt;0.001</td>
<td>15 (50.0)</td>
<td>570 (23.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>PM implantation, n (%)</td>
<td>1 (1.5)</td>
<td>84 (1.5)</td>
<td>1.00</td>
<td>0 (0)</td>
<td>13 (0.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>6 (9.1)</td>
<td>124 (2.3)</td>
<td>0.004</td>
<td>1 (3.3)</td>
<td>74 (3.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>CRT implantation, n (%)</td>
<td>6 (9.1)</td>
<td>60 (1.1)</td>
<td>&lt;0.001</td>
<td>1 (3.3)</td>
<td>7 (0.3)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Major bleeding was defined as bleeding (1) associated with a >5 g/dl (0.5 g/l) decrease in the hemoglobin level or a >15% (absolute) decrease in the hematocrit level; (2) an event that caused hemodynamic compromise; or (3) requirement for blood transfusion.

Abbreviations: CRT, cardiac resynchronization therapy; MACCE, major adverse cardiac and cerebrovascular events; SCA, sudden cardiac arrest; TIA, transient ischemic attack; other — see Table 1.

Figure 2. Kaplan-Meier curves — the NSTEMI group, mortality

Abbreviations: see Figure 1

Figure 3. Kaplan-Meier curves — the NSTEMI group, MACCE occurrence

Abbreviations: see Figure 1 and Table 1

treated invasively. It is associated with a statistically significant increase in the mortality rate and composite MACCE occurrence in patients diagnosed with STEMI and NSTEMI during 12-month follow-up. It also proves that severe MR is an independent risk factor for all-cause death.

When considering the impact of MR on patients with MI, several factors can have a significant influence on obtained results. Therefore, they have to be taken into consideration when analyzing each study concerning the subject matter. Despite the importance of the problem, the number of reliable studies analyzing this matter is limited. It is also worth mentioning that in a few studies [10, 14, 17], analyzed groups did not exceed 350 patients. Consequently, the absolute number of patients with MR is relatively low.

Nevertheless, one general conclusion is common in almost all of them [4–6, 8, 12–18] — MR has a significant influence on mortality in the group of patients after MI.

The worse prognosis for patients with MR may come from worse in-hospital characteristics, which appears to be typical of all analyzed studies [10, 12–17], including the present study. Among others, factors listed most often are advanced age [10, 12–16], CAD diagnosed in history [10, 12, 14], and diabetes mellitus [10, 14].

Even though etiology and mechanisms in which MR evolves may play an important role in analyzing the current population properly, it is hard to distinguish ischemic
mitral regurgitation (IMR) from MR caused by factors other than MI. IMR is defined as MR directly associated with CAD. IMR occurs due to ischemic myocardial changes despite unaltered mitral leaflets and chordae. LV remodeling and papillary muscle displacement are usually listed as factors playing an important role in its development [18, 29–32].

In this study, worse echocardiography results regarding LV systolic and diastolic diameters, as well as LVEF could be seen in the subgroup with severe MR, in both STEMI and NSTEMI subgroups. In connection with this, it is highly possible that most patients with severe MR from our study could be diagnosed with IMR, however, it is not possible to unequivocally confirm that assumption.

There are some differences between the present study and other available research concerning the subject matter. Most studies include in their analysis both MI types in one group [12, 15, 16], some including also unstable angina (UA) [13, 14]. Due to relevant differences in clinical course between STEMI and NSTEMI, in the present study, those two subgroups were analyzed separately. In most studies concerning this subject matter, the group diagnosed with MR is not divided according to MR severity [10], or subgroups include both moderate and severe MR [12, 13, 15, 16]. In several studies demarking a subgroup with severe MR only would probably entail creating a group composed of just a few patients, not big enough to obtain reliable results. In this study, in order to obtain unambiguous results only the patients with severe MR were taken into consideration. MI treatment methods are another factor that differentiates the compared studies.
Several of them [4, 6–9, 12] include thrombolysis, whereas, in the present study, coronary angioplasty and CABG were the only methods considered.

**Study limitations**
Several potential limitations should be borne in mind when interpreting the presented data. First, despite its high probability, we cannot confirm without fail that the index MI was the factor inducing MR. This is the limitation common to almost all studies concerning the subject matter [10–13, 15, 16]. Second, data used in this study were gathered retrospectively. Because different physicians did echocardiography examinations and MR was operator-assessed, that may lead to interpretation bias. Third, echocardiography was performed only once during the index hospitalization. Because MR grade may change in time, an echocardiography assessment during follow-up would have provided important data. Fourth, because it was not possible to obtain follow-up data from all National Health Fund departments, all analyzed follow-up data come from the regional Silesian branch of the National Health Fund.

**Clinical implications**
The present study confirms the importance of echocardiography assessment of MR in patients after MI. Taking into consideration the statistically significant findings regarding mortality in this population, special emphasis should be placed on early clinical and echocardiographic control and appropriate treatment implementation.

**CONCLUSIONS**
Mitrail regurgitation is a frequent comorbid condition in patients after MI, both STEMI and NSTEMI. It is strongly associated with more frequent HF diagnosis, higher mortality, and MACCE occurrence in a 12-month follow-up. In the population of patients after MI, severe MR is an independent risk factor for all-cause death in 12-month observation. Thus, MR assessment becomes a crucial element in determining the prognosis of MI patients.

**Supplementary material**
Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

**Article information**

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**Conflict of interest:** None declared.

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