Objective: Depression is one of the most frequent neuropsychiatric disturbances in stroke patients. The clinical aspects and correlations of depression in the first days after acute stroke are less known. This study aimed to 1) assess the frequency of depression, 2) describe the profile of depression of stroke patients and 3) analyze the relation between depression and demographic, predisposing and precipitating conditions, and clinical and imaging data, in acute stroke patients. Methods: We used the Montgomery–Asberg Depression Rating Scale to assess depression in 178 consecutive acute (≤ 4 days) stroke (26 subarachnoid hemorrhage, 31 intracerebral hemorrhage, 121 cerebral infarct) patients (mean age 57 yr) and in a control group of 50 acute coronary patients (mean age 59 yr). Results: Eighty-two patients (46%) presented acute depression; apathy/loss of interest was the most frequent clinical feature. In logistic regression, the best model to predict depression (backward model) identified previous mood disorder (odds ratio 2.2–12.9) as an independent predictor. There were no significant differences in the frequency or severity (p > 0.45) of depression between control subjects and acute stroke patients. Conclusions: Depression was present in almost one-half of the acute stroke patients and was related to previous mood disorder but not to stroke type or location. Apathy/loss of interest was the predominant clinical feature.

Introduction
Depression is one of the most frequent neuropsychiatric disturbances in acute stroke, being present in 6%–52% of acute stroke patients. Further, poststroke depression is associated with impaired recovery in cognitive function and activities of daily living and increases mortality. There are contradictory results about the location of the...
stroke lesions that are associated with depression in acute stroke. In several studies, depression was found to be most frequent and severe among patients with left anterior (cortical or subcortical) lesions, while in several case descriptions of patients with depression, acute right hemisphere lesions were more obvious. A systematic review of patients with first-ever ischemic stroke did not associate depression with any particular acute hemispheric lesion site. Two metaanalyses did not support the hypothesis that the risk of depression after stroke is due to a specific location of stroke, while a systematic review by Bhogal and others sustained that depression was related to the left hemispheric stroke.

This study aimed to assess the frequency of depression and to describe the profile of depression of stroke patients in the first 4 days after stroke. We also aimed to analyze the relation between depression and a) demographics and predisposing and precipitating conditions, b) clinical and imaging data and c) functional outcome at discharge.

Methods

We investigated prospectively the presence, severity and correlates of depression in consecutive acute stroke patients. The inclusion criteria were as follows: 1) an admission diagnosis of cerebral infarct, intracerebral hemorrhage/intraventricular hemorrhage and subarachnoid hemorrhage and 2) depression assessment performed within 4 days after stroke onset.

We excluded from the study patients who scored less than 10 on the Glasgow Coma Scale (GCS) on “eye opening” (range 1–4) and “best motor response” (range 1–6) items. We also excluded patients with a severe communication disturbance, defined as scoring 2 on the Neurological Institute Health Stroke Scale (NIHSS) on items “best language” or “dysarthria.”

The control group comprised consecutive acute coronary patients hospitalized in the Coronary Intensive Care Unit of the Hospital de Santa Maria, Lisboa, with a diagnosis of acute myocardial infarction or unstable angina. A depression assessment was performed within 4 days after onset. In addition to the exclusion criteria for stroke patients, we excluded patients with concomitant stroke.

A trained psychologist conducted this study at the Stroke Unit in the neurology department of a university hospital. Stroke patients were examined whenever possible on their first day in the stroke unit. A psychiatrist further observed the same patient if a psychiatric disorder was presumed. Previous dementia or cognitive decline, mood disorder and acute neuropsychiatric disturbances were assessed during a semistructured interview.

Patients were diagnosed as having depression if they fulfilled the Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR) criteria of Mood Disorder Due to Acute Stroke (depression), that is, if they reported and displayed depressive mood or anhedonia scoring in the items “Apparent Sadness” or “Reported Sadness” and “Inability to Feel” of the Montgomery–Asberg Depression Rating Scale (MARS) and had a MARS score of 7 points.

We used the MARS to assess intensity of depressive symptoms. We used the Gainotti’s Post Stroke Depression Rating Scale (PSDRS) to describe the profile of depressive symptoms, because this scale relies less on symptoms that can be due to stroke itself, such as vegetative and sleep disturbances. For formal global cognitive assessment, we used the Mini-Mental State Examination (MMSE), validated in the Portuguese population, taking educational levels into consideration, as previously described.

The following prestroke predisposing conditions for depression were considered: 1) dementia/cognitive decline, defined as a medical diagnosis of dementia or of mild cognitive impairment or a history of memory and another cognitive domain impairment with functional impairment in daily living activities, confirmed by a proxy; 2) alcohol abuse, defined as having at least 5 drinks daily; 3) previous stroke; and 4) previous mood disorder. Mood disorder was diagnosed if the patient had at least once in their lifetime been treated for a mood disorder and had been either prescribed specific medications for this condition, or used the medication for more than a month. The stroke symptoms fluent or nonfuent aphasia, neglect and hemiparesis were analyzed as possible predisposing variables for depression.

We defined the type and location of the stroke based on clinical data and on acute computed tomography (CT) magnetic resonance imaging (MRI). The type of stroke was defined as subarachnoid hemorrhage, intracerebral/intraventricular hemorrhage and infarct. If the CT/MRI failed to show an acute lesion, or showed only an old silent or old symptomatic lesion, location was derived from clinical data and was grouped as 1) brainstem/cerebellum, hemispherical or both and 2) left or right hemispherical or both. When the symptomatic lesion was visible on the CT/MRI, we grouped the stroke location as 1) brainstem/cerebellum, hemispherical or both and 2) left or right hemispherical or both. Hemispherical strokes were further subdivided as deep (thalamic and striatocapsular infarcts and lacunes), superficial anterior (frontal, fronto-temporal/parietal/insular) and superficial posterior (temporal, parietal, occipital or a combination of these). For statistical analyses, we considered a superficial lesion extending into the deep hemispherical structures.

We assessed functional outcome at discharge with the modified Rankin Scale (mRS). An unfavourable outcome was defined as a modified Rankin score of 3 (death or dependency). We assessed the presence and severity of depression in the control group as previously described for stroke patients.

Statistics

Data were analyzed in the Special Package for Social Sciences version 12. We used chi-square with continuity correction ($\chi^2$), odds ratios (ORs) and 95% confidence interval (95% CI) to test bivariate associations between the presence of depression and age (< 65 or 65 yr), sex and educational level (0–9 or 10 years of school, according to the minimal number of mandatory years of schooling in Portugal) and predisposing
and precipitating conditions (previous stroke, dementia/cognitive decline, mood disorder and alcohol abuse). We used the same method to test for depression, clinical symptoms and signs (apathy, neglect, hemiparesis, type (subarachnoid hemorrhage, intracerebral hemorrhage, infarct) and location (brainstem-cerebellum or hemispherical; hemispherical, left or right; hemispherical, deep or superficial; superficial, anterior or posterior) of stroke and mRS grade at discharge (0–2 or 3). We used the Mann–Whitney U test or the Kruskal–Wallis test to measure differences in MARS scores between 2 or more than 2 conditions of those categorical variables, respectively. For multivariate analysis, we used stepwise logistic regression, entering all the variables with a p < 0.15 on chi-square. Additionally, we calculated the receiver operating characteristic curves to assess the predictive value of the model. We also performed a bivariate and a multivariate analysis to analyze whether the above-mentioned variables were related to severe depression (MARS score > 19). We considered a p-value ≤ 0.05 statistically significant.

Results

From a sample of 218 stroke patients, we assessed depression in 178 acute stroke patients. We found no significant differences between included and excluded patients concerning age (p = 0.32), sex (p = 1.0) and previous mood disorder (p = 0.52). Included patients had a higher mean educational level (p = 0.01) and a lower frequency of intracerebral hemorrhage (p = 0.001) than excluded patients.

Sixty percent of our sample were men and 40% were women, both with a mean age of 56.8 years (standard deviation [SD] 13, median 57, range 24–86 yr) and a median of 4 years of school (mean 6.6, SD 5, range 0–21 yr). During the acute phase, 23% (41) of the patients were assessed in the first day, 32% (57) in the second day, 23% (41) in the third day and 22% (39) in the fourth day (mean 2.4, SD 1.1; median 2). The characteristics of the stroke are displayed in Table 1.

Thirteen percent of the patients presented a cognitive disturbance, as assessed with the MMSE (mean 25, SD 4.6, median 27, range 8–30). The median in the mRS score was 2 (range 0–6); one-third of the acute stroke patients had a poor outcome, with an mRS score > 2. Table 1. Depression was diagnosed in 82 patients (46%) (mean score 13.7, SD 6.9, median 11.5, range 7–39). The whole sample had a mean MARS score of 8.3 (SD 7.3, median 7, range 0–35). Depression was associated with female sex, hemiparesis, previous mood disorder and an mRS score > 2. Age, sex, aphasia and previous mood disorder were included in the backward regression model. The final model (R² = 0.05) included previous mood disorder as an independent predictive factor for depression (area under the ROC = 60%).

Regarding the PSDRS, the profile of the patients with depression was characterized by depressed mood, suicidal thoughts, vegetative disorders, apathy/loss of interest, anxiety, catastrophic reaction, increased emotionalism and anhedonia, which was different from the profile of the patients without depression (p < 0.01) (Fig. 1).

Table 1: Comparison between depressive and nondepressive acute stroke patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total no. (and %), n = 178</th>
<th>With depression, n = 82</th>
<th>No depression, n = 96</th>
<th>χ² (p value)</th>
<th>Odds ratio 95% CI</th>
<th>Mann–Whitney U test (p value)</th>
<th>Moderate/severe depression, n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 yr</td>
<td>55 (31)</td>
<td>26</td>
<td>29</td>
<td>0.003 (0.96)</td>
<td>1.07</td>
<td>0.57–2.03</td>
<td>3316 (0.90)</td>
</tr>
<tr>
<td>Male sex</td>
<td>106 (60)</td>
<td>46</td>
<td>60</td>
<td>0.51 (0.48)</td>
<td>0.77</td>
<td>0.42–1.40</td>
<td>2850 (0.006)</td>
</tr>
<tr>
<td>Education &lt; 10 yr</td>
<td>135 (76)</td>
<td>68</td>
<td>67</td>
<td>3.48 (0.06)</td>
<td>2.10</td>
<td>1.02–4.33</td>
<td>2351.5 (0.07)</td>
</tr>
<tr>
<td>Neglect</td>
<td>24 (13)</td>
<td>11</td>
<td>14</td>
<td>0.00 (0.99)</td>
<td>0.91</td>
<td>0.39–2.13</td>
<td>1817.5 (0.94)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>122 (69)</td>
<td>63</td>
<td>59</td>
<td>4.16 (0.04)</td>
<td>2.08</td>
<td>1.08–4.01</td>
<td>2874 (0.10)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>15 (8)</td>
<td>10</td>
<td>5</td>
<td>1.97 (0.16)</td>
<td>2.53</td>
<td>0.83–7.73</td>
<td>1104.5 (0.56)</td>
</tr>
<tr>
<td>CI/ICH/SAH</td>
<td>121/31/26</td>
<td>57/14/11</td>
<td>64/17/15</td>
<td>0.21 (0.90)</td>
<td>0.52</td>
<td>0.60–4.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Hemispherical/BC</td>
<td>100/49</td>
<td>47/23</td>
<td>53/26</td>
<td>0.00 (1.0)</td>
<td>1.00</td>
<td>0.51–1.99</td>
<td>2276 (0.54)</td>
</tr>
<tr>
<td>Left/right hemisphere</td>
<td>43/55</td>
<td>21/26</td>
<td>22/29</td>
<td>2.60 (0.27)</td>
<td>1.06</td>
<td>0.48–2.37</td>
<td>1065 (0.51)</td>
</tr>
<tr>
<td>Hemisphere superficial/deep</td>
<td>30/39</td>
<td>12/17</td>
<td>18/22</td>
<td>0.003 (0.96)</td>
<td>0.86</td>
<td>0.33–2.27</td>
<td>549 (0.80)</td>
</tr>
<tr>
<td>Superficial anterior/posterior</td>
<td>13/17</td>
<td>5/7</td>
<td>8/10</td>
<td>0.00 (1.0)</td>
<td>0.89</td>
<td>0.20–3.91</td>
<td>93.5 (0.48)</td>
</tr>
<tr>
<td>Left anterior/posterior</td>
<td>2/7</td>
<td>1/3</td>
<td>1/4</td>
<td>0.08 (0.99)</td>
<td>0.51</td>
<td>0.68–4.6</td>
<td>0.60</td>
</tr>
<tr>
<td>Right anterior/posterior</td>
<td>10/9</td>
<td>4/4</td>
<td>6/5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>33 (41)</td>
<td>15</td>
<td>18</td>
<td>0.00 (1.0)</td>
<td>0.97</td>
<td>0.45–2.08</td>
<td>2169 (0.51)</td>
</tr>
<tr>
<td>Previous dementia</td>
<td>7 (4)</td>
<td>3</td>
<td>4</td>
<td>0.00 (1.0)</td>
<td>0.88</td>
<td>0.19–4.03</td>
<td>564 (0.86)</td>
</tr>
<tr>
<td>Previous mood disorder</td>
<td>38 (22)</td>
<td>23</td>
<td>15</td>
<td>3.26 (0.07)</td>
<td>2.09</td>
<td>1.00–4.35</td>
<td>1544 (0.0001)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>66 (37)</td>
<td>26</td>
<td>40</td>
<td>1.48 (0.22)</td>
<td>0.65</td>
<td>0.35–1.20</td>
<td>3160 (0.13)</td>
</tr>
<tr>
<td>Rankin score &gt; 2</td>
<td>58 (33)</td>
<td>35</td>
<td>23</td>
<td>6.23 (0.01)</td>
<td>2.36</td>
<td>1.24–4.49</td>
<td>2511 (0.004)</td>
</tr>
<tr>
<td>Above MMSE cutpoint</td>
<td>23 (13)</td>
<td>13</td>
<td>10</td>
<td>0.84 (0.36)</td>
<td>1.67</td>
<td>0.69–4.04</td>
<td>1318 (0.10)</td>
</tr>
</tbody>
</table>

BC = brainstem-cerebellum; CI = cerebral infarct; ICH = intracerebral hemorrhage/intraventricular hemorrhage; MMSE = Mini-Mental State Examination; SAH = subarachnoid hemorrhage; χ² = χ² with continuity correction.

*Kruskal–Wallis Test.

†Stepwise regression model. Comparison between moderate/severe (cutpoint ≥ 19) depressive and non/mild depressive acute stroke patients.
Sixteen (9%) of the total stroke patients scored 19 on the MARS (moderate or severe depression). Patients with severe depression were more frequently female ($n = 11; 69\%$), had a lower educational level ($n = 16; 100\%$) and had a history of mood disorder ($n = 10; 63\%$). When we entered the variables sex, educational level and previous mood disorder, the final backward regression model ($R^2 = 0.33$) selected previous mood disorder as an independent predictive factor for moderate or severe depression (area under the ROC = 82\%).

We assessed 50 control subjects with acute coronary disease, with a mean age of 59.1 years (SD 14.2, median 60, range 34–83 yr) and a median of 4 years of school (mean 8.1, SD 5.5, range 0–17 yr). Seventy-six percent of the patients were men and 24% were women. During the acute phase, 38% (19) of the coronary patients were assessed in the first day, 22% in the second, 24% in the third and 16% in the fourth. Control subjects were more frequently male and had a lower frequency of previous alcohol abuse, compared with stroke patients (Table 2).

Twenty control subjects (40%) presented depression in the first 4 days of coronary disease. Compared with control subjects, the profile of depression in stroke patients was characterized by a higher frequency of apathy/loss of interest ($p = 0.01$) (Fig. 2). Case subjects did not have a higher frequency of depression than control subjects (OR 1.3; 95% CI 0.7–2.4). We entered the variables age, sex, educational level, previous mood disorder, stroke and coronary disease into a backward regression model. The final model ($R^2 = 0.10$) selected previous mood disorder as an independent predictive factor for depression (area under the ROC = 61\%).

**Discussion**

Depression was frequent, being present in 46\% of the acute stroke inpatients. Nine percent of the patients had moderate or severe depression. Female sex, the presence of a hemiparesis and previous mood disorder were associated with depression; the presence of a previous mood disorder was the only independent predictive factor for depression or severe depression. The profile of the patients with depression was characterized by depressed mood, suicidal thoughts, apathy/loss of interest, anxiety, catastrophic reaction, increased emotionalism and anhedonia.

The present study has some limitations, such as the exclusion of severe aphasic patients and the absence of an acute imaging exam that is more sensitive than a CT, such as diffusion MR or perfusion CT.

The use of the DSM-IV-TR depression criteria and of a validated scale as MARS, appropriate to the acute phase of stroke, allowed us to assess the prevalence and severity of acute stroke depression; the PSDRS allowed us to define the symptomatic profile of the patients with depression.

The frequency of acute poststroke depression or acute
depressive symptoms, within the first days of acute stroke, were reported in about 27%–52% of the case subjects, depending on the sample size, methodology and scale used by the researchers.\textsuperscript{2,4,6,7,35} We found a higher frequency of depression, probably because we used the DSM-IV-TR criteria of Mood Disorder Due to Acute Stroke—the most appropriate criteria for the acute phase of a stroke—and because we used a different depression scale than that reported in other studies on depression in acute stroke.

Coronary patients had the same risk of developing depression as did stroke patients, contradicting research by Aben and colleagues,\textsuperscript{2} who found that stroke patients had a risk of developing depression 1.7 times (95% CI 1.0–2.9) that of coronary patients. We assessed depression within the 4 days after stroke, whereas Aben and colleagues\textsuperscript{2} assessed depression within 1 month.

In our study, independent of the severity of depressive symptoms, previous mood disorder was the major independent predictive factor for depression. The presence of a previous mood disorder could highlight a neuropsychiatric vulnerability for ischemic stroke\textsuperscript{36} and, consequently, for acute stroke depression.

### Table 2: Comparison between mean ranks of acute stroke and acute coronary patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stroke, n = 178</th>
<th>Coronary, n = 50</th>
<th>$\chi^2$ (p value)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Mann–Whitney U test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq$ 65 yr</td>
<td>55</td>
<td>20</td>
<td>1.08 (0.30)</td>
<td>0.67</td>
<td>0.35–1.28</td>
<td>4043 (0.32)</td>
</tr>
<tr>
<td>Male sex</td>
<td>106</td>
<td>38</td>
<td>3.86 (0.05)</td>
<td>0.47</td>
<td>0.22–0.94</td>
<td>1374 (0.02)</td>
</tr>
<tr>
<td>Education &lt; 10 yr</td>
<td>135</td>
<td>32</td>
<td>1.69 (0.19)</td>
<td>1.68</td>
<td>0.85–3.32</td>
<td>3713 (0.10)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>33</td>
<td>1</td>
<td>7.29 (0.007)</td>
<td>11.23</td>
<td>1.51–84.88</td>
<td>4032 (0.004)</td>
</tr>
<tr>
<td>Previous dementia</td>
<td>7</td>
<td>4</td>
<td>0.63 (0.43)</td>
<td>0.47</td>
<td>0.13–1.70</td>
<td>1373 (0.25)</td>
</tr>
<tr>
<td>Previous mood disorder</td>
<td>38</td>
<td>13</td>
<td>0.20 (0.66)</td>
<td>0.78</td>
<td>0.38–1.63</td>
<td>301 (0.91)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>66</td>
<td>6</td>
<td>10.2 (0.001)</td>
<td>4.32</td>
<td>1.75–10.69</td>
<td>1020 (0.002)</td>
</tr>
<tr>
<td>Rankin score $&gt; 2$</td>
<td>58</td>
<td>4</td>
<td>8.54 (0.003)</td>
<td>4.83</td>
<td>1.65–14.15</td>
<td>1001 (0.0001)</td>
</tr>
<tr>
<td>MADRS score $&gt; 7$</td>
<td>98</td>
<td>24</td>
<td>0.58 (0.45)</td>
<td>1.34</td>
<td>0.72–2.52</td>
<td>1811.5 (0.55)</td>
</tr>
<tr>
<td>Depression/MADRS</td>
<td>82</td>
<td>20</td>
<td>0.36 (0.55)</td>
<td>1.28</td>
<td>0.68–2.43</td>
<td>4032 (0.004)</td>
</tr>
<tr>
<td>Above MMSE cutpoint</td>
<td>23</td>
<td>6</td>
<td>0.00 (1.00)</td>
<td>1.05</td>
<td>0.40–2.73</td>
<td>3493.5 (0.07)</td>
</tr>
</tbody>
</table>

$\chi^2 = \chi^2$ with continuity correction; MADRS = Montgomery–Asberg Depression Rating Scale; MMSE = Mini-Mental State Examination; *Stepwise regression model; U= Mann–Whitney U Test.

Despite the MADRS score, patients also had to present DSM-IV-TR criteria.

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**Fig. 2:** Profile (in %) of the cases and control subjects in the 10 items of the Post Stroke Depression Rating Scale (PSDRS). Acute stroke patients scored more frequently in the item apathy/loss of interest (*) when compared with control subjects.
As in primary depression, female sex was associated with acute stroke depression. Berg and colleagues and Carota and colleagues reported the association with female sex, but their study did not reach a significant level. Notably, there was a higher proportion of depression in older women that is perceptible in acute stroke patients, as observed by Berg and colleagues, for poststroke patients with depression.

The absence of a relation between depression and aphasia is not in agreement with the study by Carota and colleagues, who reported a borderline level of significance between overt sadness and aphasia. Kellermann and colleagues, who reported a higher depression scale score in patients with aphasia. However, in a systematic review, Bhogal and colleagues highlighted that aphasia increases the risk of developing poststroke depression but not acute stroke depression.

Left lesions have been reported as an independent factor for depression, particularly if they are small-sized lesions or if they are located in the basal ganglia (mainly in the head of the caudate) or frontal lobe. Berg and colleagues did not find an interaction between higher depression scores and lesion side, nor did Carson and colleagues in their systematic review. Berg and colleagues reported a higher nonsignificant frequency of depression after left lesion and brainstem strokes. More recently, Nys and colleagues found that, in first-ever stroke patients, a moderate or severe depression was associated with higher lesion volume but not with lesion location, previous white matter lesion or previous silent infarcts. Our research supported the systematic review by Bhogal and colleagues: we did not find a relation between acute depression and side lesion in inpatients.

In our sample, in the first 4 days after stroke, patients cried and reported sadness more frequently than previously reported. Dissociation between crying behaviour, appearance of being sad and anhedonia were described in a previous publication. Crying is associated with a patient's subjective report of feelings of sadness and with the presence of aphasia. de Coster and colleagues reported that the clinical profile of depression in acute stroke is related to depressed mood, the most sensitive symptom to the diagnosis of depression.

When compared with acute coronary patients, we found that apathy/loss of interest was the only symptom that was more frequent in acute stroke patients. Often it is stated that anhedonia is part of the concept of apathy, and is not as sensitive for the diagnosis of depression as is depressed mood. The finding that apathy/loss of interest is the only symptom that differentiated case subjects from control subjects might indicate that, although depressed mood may be a depressive reaction to a serious acute illness requiring hospitalization, apathy or anhedonia is probably related to the brain lesion.

Conclusions

Depression was present in almost one-half of the acute stroke patients and was related to previous mood disorder but not to the type or location of the stroke. The profile of depressive acute stroke patients was characterized primarily by apathy/loss of interest.

Competing interests: None declared.

Contributors: Drs. Caeiro, Ferro and Figueira designed the study. Dr. Caeiro acquired the data; Drs. Caeiro, Ferro and Santos analyzed it. Dr. Caeiro wrote the article, and Drs. Ferro, Santos and Figueira critically reviewed it. All authors gave final consent for publication.

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