Statin Therapy and Outcome After Ischemic Stroke
Systematic Review and Meta-Analysis of Observational Studies and Randomized Trials

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Background and Purpose—Although experimental data suggest that statin therapy may improve neurological outcome after acute cerebral ischemia, the results from clinical studies are conflicting. We performed a systematic review and meta-analysis investigating the relationship between statin therapy and outcome after ischemic stroke.

Methods—The primary analysis investigated statin therapy at stroke onset (prestroke statin use) and good functional outcome (modified Rankin score 0 to 2) and death. Secondary analyses included the following: (1) acute poststroke statin therapy (≤72 hours after stroke), and (2) thrombolysis-treated patients.

Results—The primary analysis included 113 148 subjects (27 studies). Among observational studies, statin treatment at stroke onset was associated with good functional outcome at 90 days (pooled odds ratio [OR], 1.41; 95% confidence interval [CI], 1.29–1.56; P<0.001), but not 1 year (OR, 1.12; 95% CI, 0.9–1.4; P=0.31), and with reduced fatality at 90 days (pooled OR, 0.71; 95% CI, 0.62–0.82; P<0.001) and 1 year (OR, 0.80; 95% CI, 0.67–0.95; P=0.01). In the single randomized controlled trial reporting 90-day functional outcome, statin treatment was associated with good outcome (OR, 1.5; 95% CI, 1.0–2.24; P=0.05). No reduction in fatality was observed on meta-analysis of data from 3 randomized controlled trials (P=0.9). In studies restricted to of thrombolysis-treated patients, an association between statins and increased fatality at 90 days was observed (pooled OR, 1.25; 95% CI, 1.02–1.52; P=0.03, 3 studies, 4339 patients). However, this association was no longer present after adjusting for age and stroke severity in the largest study (adjusted OR, 1.14; 95% CI, 0.90–1.44; 4012 patients).

Conclusion—In the largest meta-analysis to date, statin therapy at stroke onset was associated with improved outcome, a finding not observed in studies restricted to thrombolysis-treated patients. Randomized trials of statin therapy in acute ischemic stroke are needed. (Stroke. 2013;44:448-456.)

Key Words: cerebral infarction ■ ischemia ■ neuroprotective agents ■ outcomes assessment ■ stroke ■ therapy
In randomized controlled trials (RCTs), hydroxymethylglutaryl-CoA reductase inhibitors (statins) are effective for primary and secondary prevention of stroke and acute coronary events. In addition to lipid-lowering effects, statins exhibit pleiotropic actions, including vasodilatory, anti-thrombotic, anti-inflammatory, and antioxidant effects.

Experimental and clinical data also provide some evidence that statins may have neuroprotective effects after acute cerebral ischemia. In animal models, treatment with statins either before, or early after, cerebral arterial occlusion has been associated with reduced infarct volume and improved neurological function.

Data are conflicting regarding the relationship between acute statin therapy and outcome after human ischemic stroke. Some authors have reported improved survival and functional outcome associated with statin treatment, but these findings have not been consistently replicated. Interpretations can be difficult because of limited sample sizes in some reports and possible bias in statin allocation in other studies, particularly those in which statins were allocated in a nonrandomized fashion. Some authors have also reported worse outcomes in patients treated with the combination of acute statins and intravenous thrombolysis. However, these results have not been consistently reproduced.

Large randomized trials of acute statin therapy after stroke may resolve these issues, but such trials are expensive and require several years to conduct. Meta-analyses of existing observational studies and randomized trials may help to clarify the conflicting results of available data and better inform the rationale and design of large clinical trials. However, in observational studies, acute statin treatment begun after stroke onset may be biased in favor of patients with less-severe stroke, making comparisons of studies reporting poststroke statin treatment difficult to interpret. Therefore, we hypothesized that statin treatment at the time of ischemic stroke onset would be associated with greater survival and improved functional outcome at early and late follow-up, and that combination treatment with thrombolysis might alter this association.

To investigate these hypotheses, we performed a systematic review and meta-analysis of published and unpublished studies of statin treatment in acute ischemic stroke.

Methods

Search Strategy

Search terms (controlled vocabulary and free text) were identified for each of the following categories: (1) statins, (2) stroke, and (3) fatal and functional outcomes (Search Strategy in the online-only Data Supplement). These were combined to identify studies featuring statins and stroke and outcome, published before August 2011. Databases searched included PubMed, CINAHL, Embase, Scopus, Web of Science, Cochrane Library, and SciFinder Scholar. Searches were limited to human studies, published in English, in any year. Reference lists of relevant studies were searched by hand. The 2 principal investigators (D.N.C., P.K.) both reviewed titles and abstracts identified by the database searches and together decided which articles should be retrieved. These retrieved articles were reviewed by both authors to identify suitable studies. Eligibility queries were resolved by discussion to achieve consensus. In the case of published studies (including abstracts) that reported stroke outcomes according to statin use but did not meet our explicit inclusion criteria, we contacted the authors to see whether data regarding statin use and our specified outcome measures were available. Completeness of our search was ensured by searching multiple sources, including large databases, hand-searching bibliographies of published research articles and reviews, and repeating the search. Inclusion and exclusion criteria were prespecified.

Inclusion Criteria

Observational studies (prospective and retrospective) and RCTs were eligible for inclusion where outcomes of patients with ischemic stroke (incident or recurrent stroke) receiving statin therapy at the time of stroke onset were compared with those of patients not receiving statin therapy before stroke. Prespecified outcomes were death and good functional outcome, defined as a modified Rankin Score (mRS) 0 to 2, assessed at 30 days (or at hospital discharge, when 30-day outcome was not provided), 90 days, and 1 year after stroke onset. Ischemic stroke was defined according to the World Health Organization definition, with brain imaging confirmation. Studies including patients with transient ischemic attack or hemorrhagic stroke were eligible for inclusion where ischemic stroke constituted >280% of the total sample. We included studies in which other lipid-lowering agents were investigated if statins accounted for >90% of all lipid-lowering therapy. Studies were defined as prospective where data regarding statin exposure were collected before outcome status was determined, and retrospective where statin exposure data were collected after outcome status was determined. Studies restricted to patients receiving intravenous thrombolysis and statins were included and analyzed separately in a prespecified secondary analysis.

Exclusion Criteria

Exclusion criteria for our primary analysis were as follows: (1) unavailability of numbers of patients alive or with good functional outcome at 30 days (or hospital discharge), 90 days, or 1 year; (2) studies restricted to highly selected patients, such as those undergoing revascularisation for carotid stenosis, or those with cerebral vasculitis; (3) inclusion of statin therapy only as a covariate in statistical models, with neither raw data nor risk estimates relating outcomes to statin use provided; and (4) unavailability of a statin-untreated comparison group.

Primary and Secondary Analyses

In our prespecified primary analysis, we investigated the association between statin therapy at the time of stroke onset (ie, patients on statin treatment immediately before stroke onset), good functional outcome (mRS 0–2), and all-cause fatality at early and late time points after stroke. Because there may be greater likelihood of bias in observational studies, we conducted the primary analysis separately in observational studies and randomized trials.

Prespecified secondary analyses included the following: (1) studies confined to patients who received intravenous (IV) thrombolysis, categorized by statin treatment at the time of stroke onset (prestroke statin use); and (2) the association of any statin exposure in the early poststroke period (0 to 72 hours) on survival and functional outcome, regardless of whether statins were continued after stroke onset or begun de novo after stroke, because our main hypothesis was that any early statin treatment may be associated with benefit in acute ischemic stroke.

Statistical Analysis

For each study, unadjusted odds ratios (ORs) were derived from patient numbers with each outcome categorized by statin treatment. The total number included in each analysis reflects the number of patients for whom outcome data were available, which was sometimes fewer than the sum of total subjects in each of the included studies. Pooled ORs were calculated from meta-analysis of risk estimates from individual studies. For analyses of fatality, ORs <1.0 indicated lower probability of death. For analyses of functional outcome, ORs >1.0 indicated higher probability of good functional outcome (mRS 0–2).
Between-study heterogeneity was estimated using the Cochran Q test and \( \Gamma \) value. Cochran Q \( P \) values <0.1 and \( \Gamma \geq 25\% \) were considered as indicating significant heterogeneity. \[^{45,46}\] A \( P \) value threshold of <0.1 was selected because the Cochran Q test may be suboptimal at detecting true heterogeneity when the traditional threshold (\( P < 0.05 \)) for statistical significance is applied, particularly when the sample size of some studies is small or when few studies are available for analysis. \[^{45,46}\]

Where significant heterogeneity existed, pooled risk estimates were calculated using the DerSimonian-Laird random-effects model, adjusting for within-study and between-study variation. A fixed-effects (Mantel-Haenszel) model was used where there was no evidence of significant heterogeneity, adjusting for within-study heterogeneity only. Assessment of publication bias was performed using visual inspection of funnel plots, Begg rank correlation test, and Egger regression asymmetry test. Statistical analyses were performed using Stata v9.0. Sensitivity analyses were conducted to assess whether any observed associations would be affected by location (European versus non-European studies) or by proportion of patients with atrial fibrillation (\( \geq 25\% \) vs <25\%).

Because data for individual patients were not available, pooled analyses of the association between statin therapy and outcome after adjustment for other variables could not be performed. Neither was it considered valid to pool adjusted risk estimates provided in individual studies, because different independent variables were used in each of the multivariable analyses. Therefore, the results of adjusted analyses are presented separately for individual studies, along with the covariates included in each multivariable analysis.

**Results**

**Search Results**

The initial search led to identification of 13,116 paper and conference abstract titles. Review of titles and abstracts, and exclusion of duplicate studies, led to retrieval of 156 potentially eligible reports (148 articles, 8 abstracts).

For the primary analysis, 24 studies fulfilled eligibility criteria for inclusion in the primary analysis. Correspondence with authors of relevant papers yielded additional data for 12 of the previously published studies,\[^{4,17,20,21,35,47-53}\] plus 3 additional unpublished data sets (1 of which has since been accepted for publication),\[^{54}\] giving a total of 27 studies included in the primary analysis (Figure 1).

For our prespecified secondary analysis of studies of statin therapy at stroke onset in patients treated with IV thrombolysis, 5 studies were eligible for inclusion (all observational; Figure I in the online-only Data Supplement). Nine studies were eligible for inclusion in the secondary analysis of

**Figure 1.** Flow diagram of search results for primary analysis of statin at stroke onset and outcome. RCT indicates randomized, controlled trial.
poststroke statin therapy (5 observational studies, 4 RCTs; Figure I in the online-only Data Supplement).

Characteristics of the studies included in the primary analysis (statin at stroke onset and outcome) are detailed in Table I (in the online-only Data Supplement). Twenty-four were observational (23 prospective), whereas 3 were RCTs.4,31,47 In all, 113,148 patients were included, with 86,651 (76.6%) from the Swedish Stroke Registry (Riks-Stroke) and 26,497 (23.4%) from other studies. Ninety-nine percent (112,192) from the Swedish Stroke Registry (Riks-Stroke) and 26,497 (23.4%) from other studies. Ninety-nine percent (112,192) from the Swedish Stroke Registry (Riks-Stroke) and 26,497 (23.4%) from other studies.

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association persisted between statin use at stroke onset and reduced fatality at 30 days/discharge (pooled OR, 0.61; 95% CI, 0.49–0.78; P < 0.001; 16 studies, 23 186 patients) and 90 days (pooled OR, 0.82; 95% CI, 0.74–0.91; P < 0.001; 9 studies, 14 964 patients; Figure 2), but not at one year (pooled OR, 0.90; 95% CI, 0.66–1.24; P = 0.53; 7 studies, 15 013 patients).

Studies in which adjusted 90-day outcomes were reported are summarized in Table II (in the online-only Data Supplement). Although different covariates were included in each multivariable model, in most studies the association between statin therapy and good functional outcome at stroke onset was no longer apparent after adjustment for age and stroke severity.

### Randomized Trials

Of the 3 identified RCTs reporting outcome after stroke in patients randomized to statin treatment before stroke onset,43,47 only 1 included an assessment of good functional outcome at 90 days (492 patients).31 No RCT data were available for functional outcome at 30 days/discharge or 1 year. All 3 RCTs reported fatality at 90 days (956 patients), whereas 2 described fatality at 30 days/discharge and 1 year.

In the single RCT that reported functional outcome at 90 days, the OR of good functional outcome with statin use was 1.5 (95% CI, 1.0–2.24; P = 0.05; 492 patients).31 No association was observed between statin treatment at stroke onset and all-cause fatality at 30 days/discharge (pooled OR, 0.93; 95% CI, 0.60–1.43; P = 0.73; data available for 464 patients), 90 days (pooled OR, 0.98; 95% CI, 0.67–1.42; P = 0.9; 956 patients), or 1 year (pooled OR, 0.87; 95% CI, 0.57–1.31; P = 0.5; 464 patients).

### Secondary Analyses

#### Combination Therapy With Statins and Stroke Thrombolysis

Five studies (4993 patients) provided data on statin therapy at ischemic stroke onset (prestroke statin use) specifically among patients who were also treated with intravenous thrombolysis (Table III in the online-only Data Supplement).17–40 All were observational studies (3 prospective) and reported tissue plasminogen activator as the thrombolytic agent. The mean age of patients was 68.6 years, with 22.3% (1114 patients) treated with statins at onset.

In thrombolysis-treated patients, no association was observed between statin therapy and good functional outcome at 90 days (OR, 1.01; 95% CI, 0.88–1.15; P = 0.93; data available from 5 studies, 4993 patients). Statin therapy at stroke onset was associated with increased likelihood of all-cause death at 90 days (pooled OR, 1.25; 95% CI, 1.02–1.52; P = 0.03; 3 studies, 4339 patients). No functional or fatality data were available for 30 days/discharge or 1 year. In a sensitivity analysis, these findings were unchanged after exclusion of the largest study (Table IV in the online-only Data Supplement).38

Four studies reported adjusted data for 90-day functional outcome (Table V in the online-only Data Supplement). After adjusting for age, stroke severity, and other potential confounding variables, no association was observed between statin therapy at stroke onset and functional outcome in thrombolysis-treated patients (2 studies), nor between statin therapy and 90-day death (OR, 1.14; 95% CI, 0.90–1.44; 1 study, 4012 patients).38

### Poststroke Statin Treatment and Outcome

Nine studies (5 observational, 4 RCTs), including 5444 patients, reported outcome according to use of statins in the acute poststroke period (within 72 hours), including both continuation of prestroke statin treatment and statin therapy initiated de novo after stroke onset.22,23,25,34,39,53–56 The mean age of included patients was 71.3 years, with 14% to 71% treated with statins acutely after stroke.

Among observational studies, acute poststroke statin treatment was associated with good functional outcome (mRS 0–2) at 90 days (pooled OR, 1.84; 95% CI, 1.37–2.48; P < 0.001; data available from 3 studies, 1324 patients). Statin treatment in the acute poststroke period was also associated with reduced likelihood of death at 90 days (pooled OR, 0.29; 95% CI, 0.19–0.45; P < 0.001; 3 studies, 1324 patients). Similar findings were noted for both functional and fatal outcomes at 30 days/discharge and 1 year (P ≤ 0.001 for all; Table VI in the online-only Data Supplement).

In contrast, among RCTs, no benefit of acute poststroke statin treatment on 90-day functional outcome or fatality was observed. The pooled OR for good functional outcome was 1.57 (95% CI, 0.88–2.81; P = 0.12; data available from 3 RCTs, 211 subjects) and for death was 1.71 (95% CI, 0.74–3.97; P = 0.2; 3 RCTs, 146 patients).

### Analysis for Publication Bias

Inspection of funnel plots did not reveal any evidence of publication bias among observational studies or RCTs included in the primary analyses of statin treatment at stroke onset. This

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**Table. Comparison of Statin at Stroke Onset and Fatality From Observational Studies With and Without Inclusion of Riks-Stroke Data (n=86,651)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Including Riks-Stroke (n=113,148)</th>
<th>Excluding Riks-Stroke (n=26,497)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n OR (95% CI) P Value</td>
<td>n OR (95% CI) P Value</td>
</tr>
<tr>
<td>Good functional outcome (mRS 0–2)</td>
<td></td>
<td></td>
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<tr>
<td>30 days/ discharge</td>
<td>17,512 1.64 (1.14–2.36) 0.008</td>
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</tr>
<tr>
<td>90 days</td>
<td>17,606 1.41 (1.29–1.56) &lt;0.001</td>
<td>10,577 1.23 (1.08–1.61) 0.007</td>
</tr>
<tr>
<td>1 yr</td>
<td>2306 1.12 (0.90–1.40) 0.31</td>
<td>2306 1.12 (0.90–1.40) 0.31</td>
</tr>
<tr>
<td>Fatality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days/ discharge</td>
<td>109,837 0.63 (0.54–0.74) &lt;0.001</td>
<td>23,186 0.61 (0.49–0.78) &lt;0.001</td>
</tr>
<tr>
<td>90 days</td>
<td>101,615 0.71 (0.62–0.82) &lt;0.001</td>
<td>14,964 0.82 (0.74–0.91) &lt;0.001</td>
</tr>
<tr>
<td>1 yr</td>
<td>101,664 0.80 (0.67–0.95) 0.01</td>
<td>15,013 0.90 (0.66–1.24) 0.53</td>
</tr>
</tbody>
</table>
was supported by the results of Beggs and Egger tests \((P > 0.2\) for all). Similarly, there was no evidence of publication bias favoring larger positive studies of statin treatment after stroke or statin combination therapy with intravenous thrombolysis (Beggs and Egger \(P > 0.2\) for all).

For additional sensitivity analyses, please see the online-only Data Supplement.

**Discussion**

In this meta-analysis, including data from >113 000 patients, associations were seen between statin treatment at stroke onset, functional independence, and survival after stroke. These associations were most evident at early time intervals after stroke, on analysis of observational studies; we cannot rule out an association between statin therapy at stroke onset and functional outcome at 1 year. An association was also seen between statin use at stroke onset and good functional outcome \((mRS 0–2)\) in a single randomized trial, although no association was found with benefit measured by other methods (Barthel, National Institutes of Health Stroke Scale). Among observational studies, but not randomized trials, improved functional outcome and survival were also observed when statin therapy was commenced acutely (within 72 hours) after stroke onset.

It is possible that these findings represent a true benefit of statins on outcomes after stroke. This interpretation is supported by the consistency of the association between statin therapy and good outcome, and between observational studies and randomized trials. These findings are further supported by the results of animal studies, where early statin treatment has been associated with reduced infarct volume and improved neurological function. This could potentially be mediated through antioxidant, antiapoptotic, anti-inflammatory, or neuroprotective statin mechanisms or via enhanced cerebral repair. There is further support from clinical studies in which statin-treated patients show cerebrovascular benefits, including enhanced collateral circulation, improved cerebrovascular reactivity to acetazolamide challenge, and in some but not all studies, improved infarct volumes. Statins may also have indirect benefits by reducing the frequency of recurrent stroke, coronary events, and infection.

In most studies, the observed benefits of statin therapy were no longer apparent after adjustment for age, stroke severity, and other potential confounding variables. This finding might be explained if some of the observed benefit of statin therapy is mediated through an effect on stroke severity. Experimental data and some clinical studies indicate that statins may reduce infarct volume and stroke severity. However, it is also possible that statin therapy is a marker for other factors related to improved stroke outcome. We cannot fully exclude the possibility that undetected bias or confounding may contribute to the observed association. Statin treatment has been associated with greater prevalence of factors such as diabetes mellitus and atrial fibrillation, which are associated with poorer outcome after stroke, but statins may also be associated with unmeasured factors that may promote favorable outcome such as better socioeconomic status, medication compliance, lifestyle habits, or health-care access. Such a healthy cohort effect is a recognized difficulty in interpreting studies of treatment effects.

We also acknowledge the possibility of undetected bias in statin prescribing (confounding by indication). This is most likely to occur in observational studies of patients prescribed statins after stroke onset, where patients with milder stroke severity are more likely to be prescribed statins for secondary prevention. This may partially explain the difference in benefit seen between studies in which patients were treated with statins at stroke onset, and those where statin treatment was begun (or continued) after stroke had occurred. However, the influence of stroke severity on physician prescribing is unlikely to account for the benefits seen in patients on statins before the stroke occurred. The consistent benefit observed among observational studies and randomized trials of patients on statin treatment before the onset of their stroke, supported by pathophysiological data from experimental and human imaging studies, also suggest that these findings may not be fully explained by prescribing bias. Any association between prestroke statin use and outcomes is not only of clinical interest, but also provides a rationale for investigation of acute post-stroke statin use, as if a neuroprotective effect is exerted by statins taken before the onset of stroke, it is possible that statins given very early after stroke might exert a similar benefit.

In contrast to studies of unselected patients, we found no association between statin therapy and improved functional outcome in studies limited to patients treated with tissue plasminogen activator. In unadjusted analyses, we found higher early fatality rates in this group, although this association was not observed after adjustment for potential confounders. Conflicting data have been reported on outcomes of patients receiving combination therapy with statins and tPA. Some studies have suggested that statin use at stroke onset may be associated with increased rates of symptomatic intracerebral hemorrhage (ICH) after intravenous or intra-arterial thrombolysis. In RCTs, a small increased risk of ICH associated with statin therapy has also been observed in tPA-untreated patients, possibly mediated via antithrombotic effects of statins on endothelium, leucocytes, and platelets, and increased levels of endogenous tPA. Others have not confirmed an independent association between prestroke statin use and post-thrombolysis ICH after adjustment for factors known to increase ICH risk, similar to findings in the largest study of tPA-statin combination therapy included in our meta-analysis. Randomized trials and individual-patient data from large registries will be required to resolve this issue.

Two recent studies, published after completion of our systematic review, also reported an association between early statin treatment and improved outcomes. The relationship of statins and early functional stroke outcome has also been the subject of an earlier meta-analysis, in which an association between statin therapy and good functional outcome was also reported (pooled OR, 1.62; 95% CI, 1.39–1.88). Although this provided valuable information, it included relatively few patients (11 695 patients from 12 studies), from observational studies only, with heterogenous definitions of outcome. By comparison, strengths of our analysis include the large sample size (32 studies, 118 000 patients overall), inclusion of published and unpublished data, stratification by observational
and randomized trial design, standardized outcome definitions (including fatality), and analysis of early and late outcomes. We performed sensitivity analyses to assess whether results were primarily influenced by single large studies and analyzed studies of tPA-treated patients separately. To aid interpretation, we further reported adjusted analyses for individual studies, but did not pool results because these studies adjusted for differing predictor variables.

We acknowledge some limitations. Few randomized trials were available, and consequently, most data included were from nonrandomized observational studies. However, although observational studies may be subject to undetected bias, their findings complement data from RCTs and experimental studies. Findings from observational studies may also suggest benefits or adverse effects of medications not detected in randomized trials, and may provide useful information about medication effects in clinical practice.63-67 We acknowledge that reproducibility of our analysis could be limited by the inclusion of unpublished data, although these data came from well-recognized large registries. Other limitations are unavailability of information regarding cause of death and stroke recurrence stratified by statin treatment, and unavailability of individual-patient data to establish the influence of statin withdrawal, dose-response relationships, or any association between lipophilic status and outcome.

Despite these caveats, the findings from this comprehensive literature review and meta-analysis of multiple studies, including a large number of stroke patients, suggests a relationship between statins and improved stroke outcome. We emphasize that we do not recommend routinely prescribing statins for acute neuroprotection. Because this was an exploratory analysis based on largely observational studies, with inherent limitations, it remains unclear whether very early statin use after ischemic stroke provides benefit compared with commencement later during hospitalization, nor do these data indicate that thrombolysis should be withheld in otherwise eligible statin-treated patients with acute ischemic stroke. Rather, when taken together, our data provide a compelling case underlining the need for large randomized trials to further investigate the efficacy and safety of statin therapy in acute ischemic stroke. Ongoing studies such as NEUSTART II (Neuroprotection with Statin Therapy for Acute Recovery Trial II), EUREKA (The Effects of Very Early Use of Rosuvastatin in Preventing Recurrence of Ischemic Stroke) and STARS07 (Stroke Treatment with Acute Reperfusion and Simvastatin) may provide valuable safety and efficacy information in this regard.68-71

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