Age-Dependent Effect of β-Blockers in Preventing Vasovagal Syncope

Robert S. Sheldon, MD, PhD; Carlos A. Morillo, MD; Thomas Klingeneheben, MD; Andrew D. Krahn, MD; Aaron Sheldon, BSc; M. Sarah Rose, PhD

Background—β-blockers have little effectiveness in preventing vasovagal syncope in unselected populations, but they might be effective in older patients. We determined whether β-blockers prevent vasovagal syncope in an age-related fashion.

Methods and Results—Two populations were studied. A proportional hazards analysis was performed on an observational cohort study of 153 patients with vasovagal syncope, 52 of whom received β-blockers. A multivariable proportional hazards model stratified by center was performed on 208 participants in the randomized Prevention of Syncope Trial (POST), examining the interaction between age group and treatment with metoprolol. Age-specific hazard ratios were estimated for both studies and combined using the inverse variance meta-analytic method. In the cohort study, the hazard ratio for syncope if treated with β-blockers was 1.54 (95% CI, 0.78–3.05) for patients aged <42 years and 0.48 (95% CI, 0.12–1.92) for patients aged ≥42 years. In POST, the proportional hazards model showed interactions between age and treatment effect (P=0.026). The hazard ratio for patients aged ≥42 years who received metoprolol was 0.53 (95% CI, 0.25–1.10); in patients aged <42 years, the hazard ratio was 1.62 (95% CI, 0.85–3.10). A pooled analysis of both studies yielded an estimate of the hazard ratio of 1.58 (CI, 1.00–2.31) for patients aged <42 years, and the hazard ratio was 0.52 (CI, 0.27–1.01) for patients aged ≥42 years. The 2 age groups differed significantly in response to β-blockers (P=0.007).

Conclusions—β-blocker treatment may suppress vasovagal syncope in middle-aged patients aged ≥42 years. (Circ Arrhythm Electrophysiol. 2012;5:920-926.)

Key Words: aging ■ β-blockers ■ clinical trials ■ syncope

Vasovagal syncope is a common clinical problem that frequently proves difficult to treat. One of the earliest treatments to be attempted was β-receptor blockade.1 After initial enthusiasm,2–4 this treatment was questioned5,6 and subjected to at least 5 randomized clinical trials, with syncope as the primary outcome.47–10 They culminated in little evidence for the effectiveness of β-blockers in preventing vasovagal syncope in the general population. These results were surprising, given the ability of isoproterenol to induce syncope on tilt-table tests2,11 and the large volume of evidence that β-blockers prevent positive responses to tilt-table testing.12

One explanation might be an age-dependent effect of β-blockers in preventing the vasovagal reflex. Natale et al13 reported an observational study of 112 patients who were treated with metoprolol.13 Patients appearing to respond to metoprolol were older (55±12 years versus 42±15 years), and age ≥42 years was associated with a lower likelihood of syncope on metoprolol. Similarly in a small study of 32 subjects, Leor et al14 reported that patients appearing to respond to metoprolol were older (28±4 years versus 22±3 years).

To test the hypothesis that β-blockers prevent syncope recurrences in older patients, we performed analyses on 2 separate populations and then pooled the results using a meta-analytic method using variance-weighted least squares. The first study was an observational cohort,6,15,16 and the second was a randomized controlled trial (RCT), the Prevention of Syncope Trial (POST),9,17 in which patients were randomized to receive metoprolol or placebo. In a prespecified and stratified analysis, there was a trend toward benefit in older subjects in POST. Here, we assess whether there was an age-dependent effect in the observational cohort and then use a meta-analysis to provide a point estimate and CIs of the effect for the total population of cohort and randomized studies.

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Methods

Observational Cohort Study

The observational cohort6,15,16 from Southern Alberta was enrolled and followed between January 1989 and December 2002. The global population consisted of 227 sequentially consenting patients referred for the assessment of syncope who underwent tilt-table testing if they had any one of the following: (1) ≥2 syncopal spells; (2) 1 syncopal episode and ≥4 presyncopal episodes; or (3) a single episode of syncope causing serious injury. One hundred fifty-three patients had
positive tilt-table tests, and 74 had negative tests. Only the 153 patients with a positive tilt test were included in this analysis to align them with the POST population, all of whom had positive tilt tests. After passive head-up tilt testing with or without subsequent isoproterenol infusion if the first stage was negative, 52 patients were subsequently treated at the physician’s discretion using the limited contemporary understanding of patient and treatment selection with β-blockers, and 101 remained drug-free. The mean daily doses of the drugs used were as follows: atenolol 47.5 mg (n=30), metoprolol 105 mg (n=10), propranolol 71.4 mg (n=7), nadolol 93.3 mg (n=3), timolol 20 mg (n=1), and pindolol 20 mg (n=1). There were no evidence-based guidelines at the time. All patients were asked to notify the syncope clinic of their first occurrence of syncope, and all patients were also contacted every 6 months. They were followed up for up to 47 months. Syncope was defined for the patients as a complete loss of consciousness resembling the syncope that led to their assessment.

POST Randomized Controlled Trial
The multicenter POST was a randomized, placebo-controlled, double-blind trial designed to assess the effects of metoprolol in vasovagal syncpe. The population was enrolled and followed for up to 1 year between October 1998 and April 2004 and was described in detail elsewhere. The POST subjects were from 5 countries: Canada (151), Germany (26), Columbia (15), United States (14), and Australia (2). The study was approved by the University of Calgary Conjoint Health Research Ethics Board and by the institutional reviewing boards of all participating institutions. The University of Calgary Syncope Clinic coordinated the trial and managed data storage and analysis. Patients were eligible for randomization in POST if they had a positive response to passive head-up tilt with or without subsequent isoproterenol infusion if the first stage was negative, and one or both of ≥3 lifetime syncopal spells preceding the tilt test (n=206), or ≥1 syncope recurrence within 6 months of a positive tilt test (n=2). An earlier unpublished analysis of the cohort study with all 227 patients from the syncope clinic showed evidence of a significant interaction between (log) age and β-blocker use (P=0.016). The hazard ratio for treatment with β-blockers depended on the age of the patient. Younger patients were more likely to faint when treated with β-blockers, whereas older patients were less likely to faint. The instantaneous risk was equal to 1 when the age was ≥42 years, and therefore randomization in POST was stratified according to ages <42 and ≥42 years. Patients were excluded if they had other causes of syncope, could not give informed consent, had important noncardiovascular or cardiovascular diseases or a permanent pacemaker, had a pressing need for or contraindication to β-blockers, or had used β-blockers at a dose greater than the equivalent of metoprolol 25 mg BID for the purpose of suppressing the symptoms of vasovagal presyncope or syncope. Syncope was documented in a case report form and adjudicated by an outcomes adjudication committee.

Statistical Analysis
For this analysis, the cohort was limited to patients with a positive tilt-table test (n=153). The characteristics of patients in the cohort who were treated using β-blockers versus those not treated by β-blockers were described using the median (interquartile range) for continuous variables and percentages for categorical variables and compared using t tests for normally distributed variables (after applying a logarithmic transformation where necessary) and Fisher exact tests for categorical variables. Characteristics of the POST population were described similarly, but differences between the arms were not tested because this was a randomized clinical trial. Differences in treatment effect for both studies were illustrated using Kaplan-Meier syncope-free survival curves.

Proportional hazards analysis was used to analyze outcomes. The proportional hazards model is a regression model for survival data. The hazard rate is a function of follow-up time and is the number of events observed (here first syncope) per unit time divided by the number at risk. In proportional hazards regression, the natural logarithm of the hazard function at any time is modeled as the (log) baseline hazard multiplied by a linear function of the predictor variables (similar to that in linear regression). The effect of a variable on outcome is then assessed by the statistical significance of its coefficient. The exponential of the coefficient is termed the hazard ratio and can be interpreted similar to the odds ratio as a comparison of risk between the 2 groups.

As explained in the CONSORT statement, the strongest analyses of a difference in treatment effect in complementary subgroups should be based on a test of interaction, not on the examination of P values of the treatment effect in subgroups. Thus, in both the analysis of the cohort study and in POST, the primary analysis of interest is the test of significance of the interaction term between β-blocker use and age group, using a proportional hazards model predicting time to first syncope. Patients who did not faint within the respective follow-up periods were censored. During model building in the cohort study, because of the lack of power with a small sample size, a P value of 0.10 for interaction was considered preliminary evidence of a significant age-dependent effect of treatment with β-blockers. For the POST study, a more stringent P value of 0.05 was considered significant. For the POST analysis, the proportional hazards model was stratified by center. Schoenfeld residuals were used to examine the assumption of proportional hazards. There was no evidence against the assumption of proportional hazards for any of the variables in the model (P>0.05). For both studies, age was stratified at 42 years to align with the randomization for POST. Age-specific (<42 and ≥42 years) hazard ratios (with 95% CIs) were estimated from the proportional hazards analysis for each study and after assessing the within-age group heterogeneity were combined using inverse variance analytic method, and differences in the summary hazard ratios between the 2 age groups were tested using variance-weighted least squares.

Results
Observational Cohort
In the cohort population, there were 153 patients, 52 of whom were treated with β-blockers (Table 1). Patients treated with β-blockers were older than those not treated with β-blockers (P=0.028) and had a higher frequency of syncopal spells (P=0.018). Kaplan-Meier curves showing the difference in syncope-free survival for the 2 age groups are presented in Figure 1. When examined in this group of 153 patients with positive tilt tests, the interaction between (log) age and β-blocker use approached significance (P=0.053). When the binary variable for age was used (<42 years and ≥42 years) in the interaction, the P value was larger (P=0.140), with wide CIs for the hazard ratio estimates. From this proportional hazards model, the estimated hazard ratio for patients aged <42 years is 1.54 (CI, 0.78–3.05) and for patients aged ≥42 years is 0.48 (95% CI, 0.12–1.92).

Randomized Trial Population
In the POST population, there were 208 patients, of whom 108 received β-blockers and 100 did not. The mean age was 42±18 years, and 134 were women (64%). During a median follow-up duration of 143 days, 39 patients (36%) treated with β-blockers had at least 1 syncopal spell, and 36 patients (36%) not treated with β-blockers had a syncopal spell. The Kaplan-Meier estimates of syncope-free survival for POST are presented in Figure 2. In the proportional hazards model predicting syncope recurrence, stratified by center, the interaction between age group and β-blocker use was significant (P=0.026). The hazard ratio for patients aged ≥42 years who received metoprolol was 0.53 (95% CI, 0.25–1.10),
whereas in patients aged <42 years, the hazard ratio was 1.62 (95% CI, 0.85–3.10) (Table 2).

## Combined Populations

Using variance-weighted least-squares regression, there was a significant difference in response to β-blockers between age groups in the combined hazard ratios (test for interaction \(P=0.007\)). The estimated treatment hazard ratio in the younger group was 3.03× that in the older group (95% CI, 1.36–6.67).

### Table 1

Baseline Characteristics of the 153 Participants in the Observational Cohort Study According to Whether They Were Treated With β-Blockers or Not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β-Blockers</th>
<th>No β-Blockers</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>52</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>38 (26–58)</td>
<td>33 (20–50)</td>
<td>0.028</td>
</tr>
<tr>
<td>Women</td>
<td>22 (42)</td>
<td>43 (43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tilt test outcome: syncope</td>
<td>32 (62)</td>
<td>49 (49)</td>
<td>0.171</td>
</tr>
<tr>
<td>Lifetime syncopal episodes</td>
<td>5 (2–25)</td>
<td>4 (2–17)</td>
<td>0.744*</td>
</tr>
<tr>
<td>Duration of symptoms, mo</td>
<td>24 (6–75)</td>
<td>32 (6–84)</td>
<td>0.626*</td>
</tr>
<tr>
<td>Frequency of spells, spells/mo</td>
<td>0.50 (0.16–1.15)</td>
<td>0.25 (0.10–1)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Tilt test peak heart rate, bpm</td>
<td>140 (119–147)</td>
<td>130 (115–150)</td>
<td>0.142</td>
</tr>
<tr>
<td>Tilt test peak systolic blood pressure, mm Hg</td>
<td>127 (107–143)</td>
<td>123 (108–137)</td>
<td>0.708</td>
</tr>
<tr>
<td>Tilt test trough heart rate, bpm</td>
<td>70 (60–88)</td>
<td>70 (61–80)</td>
<td>0.474</td>
</tr>
<tr>
<td>Tilt test trough systolic blood pressure, mm Hg</td>
<td>62 (51–74)</td>
<td>61 (52–76)</td>
<td>0.813</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; IQR, interquartile range.

The results are presented as medians with IQRs for continuous variables and n (%) for categorical variables.

\(P\) values are for the t test for continuous variables (*logarithm-transformed variable) and Fisher exact tests for categorical variables.

Discussion

This analysis of 2 distinct study populations revealed a markedly age-dependent effect of β-blockers on the likelihood of a syncope recurrence in patients with vasovagal syncope. Despite differences between the populations and the structures of the studies, the results were similar. The age effect in the observational cohort has not been reported previously, and the meta-analysis provides a point estimate of the effect for the total population, while revealing almost no heterogeneity between the two quite different studies. In patients aged ≥42 years, the instantaneous risk of a syncope recurrence was reduced by 48%, whereas in patients aged <42 years the risk of a syncope recurrence was increased by 58%.
were older than those who did not respond. The general lack of effective medical treatment for vasovagal syncope, coupled with the observations of Natale et al and Leor et al, prompted us to stratify patients before randomization in the POST study according to ages <42 and ≥42 years. As hypothesized, there was a significant age-dependent effect.

A similar effect was noted in the observational cohort study. This is reassuring for several reasons. The population was from a different era, having been enrolled 10 years before the randomized study. The patients were enrolled based on clinical judgment, in the context of contemporary general medical sense. Finally, it represents a real-life patient population, without the well-known limitations of the setting of a formal RCT.

**Clinical Implications**

Taken together, the studies are internally consistent and suggest that β-blockers may be effective in older patients but should not be generally used in younger patients. If so, they will prove to be a useful addition to medical treatment. Only midodrine has reasonable evidence of effectiveness, and it cannot be used in patients with hypertension. It is the subject of POST 4, a randomized placebo-controlled study of midodrine in moderately severe vasovagal syncope. Fludrocortisone was recently assessed in POST 2, a randomized placebo-controlled study of fludrocortisone in moderately severe vasovagal syncope, and also should not be used in patients with hypertension. Permanent pacing is effective in highly selected patients with documented asystole during clinical syncope. The formal demonstration of the effectiveness of β-blockers will require a randomized clinical trial in patients aged ≥40 years.

**Physiological Insights**

The source of this age-dependent effect is uncertain. There are no age-dependent effects on trough blood pressure or trough heart rate at the time of presyncope and syncope during passive and nitroglycerin tilt tests, suggesting that the age-dependent effect lies upstream. The β1- and β2-adrenoceptors both diminish with age, with a commensurate loss in responsiveness to catecholamines. Notably, older patients are also less likely to have a positive isoproterenol tilt-table test, have a slower progression of symptoms during the test, and are more likely to develop presyncope than syncope. This alone does not explain the clinically observed effect.

It may be that a proportion of older patients have age-related orthostatic intolerance and that this is more easily prevented than is vasovagal syncope of younger patients. There is still some debate as to whether these are separate disorders or simply age-related manifestations of the same disorder. However, both older and younger patients have the same age of onset of syncope, arguing for a single disorder.

This unusual effect may arise because of the complex interaction of the adrenergic receptor systems with the venous system. Shigemi et al reported that β-receptor activation had no direct effect on unstressed venous volume but it dilated hepatic outflow resistance during hypotensive stress. This was opposed by α-adrenergic–mediated constriction. β-blockade caused a large increase in venous volume, presumably by uncovering α-adrenergic–mediated hepatic venous outflow.

Table 2. Baseline Characteristics of the 208 Participants in the POST Randomized Clinical Trial According to Whether They Were Treated With β-Blockers or Not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β-Blockers</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td>Age, y</td>
<td>40 (27–58)</td>
<td>36 (25–53)</td>
</tr>
<tr>
<td>Women</td>
<td>66 (61)</td>
<td>68 (68)</td>
</tr>
<tr>
<td>Positive drug-free test</td>
<td>46 (43)</td>
<td>45 (45)</td>
</tr>
<tr>
<td>Lifetime syncopal episodes</td>
<td>8 (4–20)</td>
<td>9 (5–20)</td>
</tr>
<tr>
<td>Duration of symptoms, y</td>
<td>12.5 (3.3–30.1)</td>
<td>10.1 (3.2–20.3)</td>
</tr>
<tr>
<td>Frequency of spells, spells/yr</td>
<td>1.2 (0.3–3.9)</td>
<td>1.2 (0.6–4.4)</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>70 (61–76)</td>
<td>72 (65–79)</td>
</tr>
<tr>
<td>Supine systolic blood pressure, mm Hg</td>
<td>125 (116–138)</td>
<td>120 (110–132)</td>
</tr>
</tbody>
</table>

POST indicates Prevention of Syncope Trial; bpm, beats per minute; IQR, interquartile range.

The results are presented as medians with IQRs for continuous variables and n (%) for categorical variables. Baseline differences were not reported in accordance with the CONSORT guidelines, although no significant differences were found on post hoc analysis.

**β-Blockers and Vasovagal Syncope**

After early promise of effectiveness, β-blockers were not found to have therapeutic benefit in 5 randomized clinical trials, with syncope as the primary outcome. The β-blockers in the studies include atenolol, metoprolol, propranolol, and nadolol. The study populations included patients with a wide range of ages, and none of the studies reported an age-dependent effect. (We attempted a patient-specific meta-analysis of extant databases but were unable to merge the databases.) The mean ages in the studies ranged from 32 to 44 years. However, both Natale et al and Leor et al reported in small, nonrandomized studies that patients who seemed to respond to β-blockers...
resistance. Given that venous capacitance declines with age,\textsuperscript{35} it may be that $\beta$-blockade worsens syncope by causing an increase in the venous volume that precedes syncope.\textsuperscript{36} Older patients would be spared this deleterious effect and have a beneficial response, possibly because of blockade of the $\beta$-adrenergic effect on central cardiopulmonary baroreceptors. Finally, there may be an age-independent effect at another site that does not diminish with age.\textsuperscript{37}

Analytic Method

RCTs are the gold standard for estimating treatment effect, but because the randomized sample is almost never a random sample of the population of interest, results may lack generalizability. Observational studies, on the other hand, can suffer from bias because of nonrandom assignment but are, in general, more representative of the target population. Thus, consideration of RCTs alone may be appropriate when assessing the efficacy of the treatment, but assessment of the effectiveness within a more general target population can be improved by considering the evidence from observational studies. The concept of complex synthesis (ie, combining results across different study types) has received much attention recently in the development of statistical methodology.\textsuperscript{38,40} Applications of this methodology have been published for cardiovascular events,\textsuperscript{41} and complex synthesis is recommended for the assessment of adverse events.\textsuperscript{42}

The analysis presented here is a simple example of a meta-analysis across different study types but with only 1 study within each study type. We initially considered using a random effects model, whose assumptions include random effects within multiple studies of the same study type. However, this would not be appropriate because here there is only 1 study within each study type. Therefore, the random effects model was replaced by a fixed effects model, and the combined treatment effect was estimated using variance-weighted least squares.

Two findings attest to the robustness of this approach. Not only was there no evidence of heterogeneity between the 2 studies, but the same results were obtained from a randomized population selected using strict inclusion and exclusion criteria and from a less exclusive, broadly based clinic population.

Tests of Statistical Significance

The CONSORT statement\textsuperscript{19} provides for analyses such as these by explicitly stating that the strongest analysis of a difference in treatment effect (here, $\beta$-blockers) is with a test of interaction. With this, it is appropriate to use a single $P$ value from the interaction term in the proportional hazards regression model and not the examination of the separate statistical significances of the treatment effect in subgroups. The measurement of treatment effect here is the hazard ratio, and therefore the difference in treatment effects between the 2 groups is a comparison of the hazard ratios in the younger group and the older group, which is provided by the coefficient for the interaction term (between treatment and age group) in the model. We provided the $P$ value for the interaction term in each analysis (cohort, POST, combined) but did not present the CI because the interpretation of the single interaction coefficient is not meaningful. Instead, we used the estimated regression coefficients to estimate the hazard ratio in each group involved and the 95% CIs for each hazard ratio.

Limitations

The upper limits of the CIs of the pooled effect estimates hovered at 1.0, and this dampens the strength of our conclusions. The observational cohort study was not randomized, and there was no formalized treatment routine. This did introduce at least one confounding influence, because patients who had a positive tilt test, a higher peak heart rate, or a lower trough blood pressure were more likely to receive $\beta$-blockers. Patients in the observational studies were not treated with maximum doses of $\beta$-blockers, although the doses were similar to those used in other studies. In POST, we used only metoprolol, which is hydrophilic and $\beta_1$-selective, whereas the observational study used 6 $\beta$-blockers. However, 40 of 52 patients used metoprolol or atenolol, both hydrophilic and $\beta_1$-selective. There is some evidence that hydrophobic or nonselective $\beta$-blockers are more effective in preventing syncope during tilt testing.\textsuperscript{12} Only passive and isoproterenol tilt tests were used in POST, and this might have inserted a selection bias. Indeed, Delépine et al\textsuperscript{80} reported only partial agreement in tilt test outcomes when comparing isoproterenol versus nitroglycerin in the same patient. However, almost all patients who had a positive test without provocative medication also fainted after nitroglycerin provocation, and POST 1 included patients with positive responses to either passive tilt or isoproterenol tilt testing. POST 1 also reported similar outcomes in patients with either passive or isoproterenol tilt tests. However, nitroglycerin tilt tests were not used in POST 1, and therefore it is not known whether older patients with positive nitroglycerin tilt tests respond to $\beta$-blockers. Complicating all of this is the recommendations of guidelines to use the history to establish the diagnosis and only use tilts where reasonable doubt persists.\textsuperscript{43}

The cohort population was selected based on best clinical judgment from 1989 to 1992, without formal diagnostic criteria. However, patients with positive and negative tilt tests were very similar in baseline clinical and demographic characteristics and clinical outcome. Furthermore, a multivariable regression model using the baseline characteristics predicted outcomes equally well in the populations with positive and negative tilt tests. These findings suggested that the 2 populations were very similar, and the only detectable difference between the 2 was tilt test outcome. A secondary analysis in the Syncope Symptom Study supported this conclusion.\textsuperscript{44} Therefore, the observational cohort included a large majority of patients with vasovagal syncope.

Conclusion

$\beta$-blockers may be effective in preventing syncope in older patients (aged $\geq$42 years) and should not be used in younger patients.

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Disclosures
None.

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37. Mak A, Cheung MW, Ho RC, Cheak AA, Lau CS. Bisphosphonates and atrial fibrillation: Bayesian meta-analyses of randomized...
Syncope affects ≈50% of adults, is the cause of 1% to 2% of emergency room visits, and probably is responsible for $2.4 billion in US healthcare costs yearly. Vasovagal syncope is the most common type and can be provoked by isoproterenol during tilt-table tests. Despite the ability of β-blockers to prevent syncope during tilt-table testing, these drugs failed to reduce syncope in randomized trials. Three observational studies hinted that β-blockers might prevent syncope mainly in older subjects. We assessed whether there was evidence of an age-dependent effect of β-blockers in the randomized Prevention of Syncope Trial and an earlier observational study, by performing a meta-analysis. The estimate of the hazard ratio of β-blockers on syncope for patients aged <42 years was 1.58 (CI, 1.00–2.31) but was 0.52 (CI, 0.27–1.01) for patients aged ≥42 years. In a test of interaction, the 2 age groups differed significantly in response to β-blockers (P=0.007). These results raise the possibility of preventing vasovagal syncope in older patients with β-blockers. Randomized trials that focused on β-blockers in the older population are warranted.
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