Sulfonylurea Use Before Stroke Does Not Influence Outcome

Christopher G. Favilla, BA; Michael T. Mullen, MD; Myzoon Ali, PhD; Peter Higgins, MD; Scott E. Kasner, MD; on behalf of the Virtual International Stroke Trials Archive (VISTA) Collaboration*

Background and Purpose—Sulfonylureas block nonselective cation channels and lower serum glucose and are neuroprotective in animal models of ischemic stroke. Human data on sulfonylureas in acute stroke are sparse and conflicting. We aimed to measure the potential neuroprotective effect of prestroke sulfonylurea use in diabetic patients.

Methods—We analyzed data from a prospective cohort of individuals with diabetes mellitus (DM) enrolled in nonreperfusion ischemic stroke trials within Virtual International Stroke Trials Archive (VISTA) comprising 1050 patients, 298 with sulfonylurea use before stroke onset. The primary outcome measures were baseline National Institutes of Health Stroke Scale score and 90-day modified Rankin Scale score.

Results—Compared with patients on no DM medications, those with sulfonylurea use before stroke onset presented with less severe stroke (OR, 0.69; 95% CI, 0.53 to 0.89) but had similar modified Rankin Scale scores at 90 days (OR, 0.95; 95% CI, 0.74 to 1.23). Compared with those on other DM agents, there was no difference in initial stroke severity (OR, 1.04; 95% CI, 0.73 to 1.48) nor modified Rankin Scale score at 90 days (OR, 1.00; 95% CI, 0.71 to 1.40). Compared with those using any DM medication, patients not on any treatment experienced higher initial National Institutes of Health Stroke Scale scores (OR, 1.48; 95% CI, 1.18 to 1.86) and were marginally more likely to have poor outcomes (modified Rankin Scale score >2) at 90 days (OR, 1.31; 95% CI, 0.97 to 1.77).

Conclusions—Sulfonylurea use before stroke onset did not affect stroke severity or long-term functional outcome compared with other DM treatments. This finding casts doubt on the use of sulfonylureas for prophylactic neuroprotection. Furthermore, patients not using any medication for DM appear to have more severe strokes and worse outcomes. (Stroke. 2011;42:710-715.)

Key Words: diabetes mellitus ■ neuroprotection ■ stroke ■ sulfonylurea

A cute stroke is the third leading cause of death and a leading cause of acquired disability in industrialized nations. The presence of hyperglycemia and diabetes mellitus (DM) more than doubles the risk of ischemic stroke, and strokes experienced by diabetics are associated with a worse outcome.1–4

Oral sulfonylurea (SU) use is common among diabetics, and these drugs have 2 potential mechanisms for neuroprotection. They bind to the SU receptor 1 in pancreatic β cells to enhance insulin secretion by inhibiting adenosine 5’-triphosphate-dependent potassium channels, thereby improving glycemic control. SU receptor 1 also regulates a nonselective cation (NCa-ATP) channel, which is expressed in the central nervous system under ischemic conditions.5–7 Adenosine 5’-triphosphate depletion triggers NCa-ATP channel opening, instigating oncotic cell death and cytotoxic edema.8 Poststroke administration of SUs has been shown to block NCa-ATP channels and to decrease mortality, infarct volume, and cerebral edema in a rodent model of stroke without a substantial hypoglycemic effect.7

Human data on SUs in acute stroke are sparse and conflicting. In 1 observational human study, patients with DM who were taking SUs before stroke onset experienced no significant neurological improvement compared with those not on these agents.9 More recently, a small cohort of patients with stroke with Type 2 DM who were taking SUs appeared to experience greater clinical improvement than those who were not taking SUs independent of glycemic control.10 In this cohort, no long-term follow-up data were collected, and moderate to severe strokes (initial National Institutes of Health Stroke Scale [NIHSS] >9) were excluded from the analysis. Consequently, the influence of preischemic SU use on initial stroke severity could not be assessed.

The potential role of SUs as neuroprotective agents deserves further investigation. The aim of the current study was to explore the potential neuroprotective effect of prestroke

Received August 9, 2010; accepted September 13, 2010.

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.110.599274
SU use among patients with DM. The Virtual International Stroke Trials Archive (VISTA) database provides a large cohort for analysis and systematically collected outcome data, which was not available in previous studies. We hypothesized that use of a SU drug before stroke onset would convey clinical benefit as measured by lower initial stroke severity and improved long-term functional outcome.

Patients and Methods

We analyzed the data from a prospective cohort comprised of individuals with DM enrolled in nonreperfusion ischemic stroke trials within VISTA. Subjects with DM were included from any placebo arm as well as any therapeutic arm that found no effect, defined as P>0.30 for an individual trial, or P>0.10 in a subsequent meta-analysis of trials for a particular agent. Inclusion was dependent on availability of data describing demographic features, comorbidities, baseline medication use, baseline deficit (NIHSS), and outcome (modified Rankin Scale [mRS]) data up to 90 days postenrollment.

Exposure was defined as second- or third-generation SU (glipizide, gliclazide, glibenclamide/glyburide, glibendiamide, metahexamide, glibidine, and glimepiride) use before stroke onset. The patient must have reported use of 1 of these agents at baseline before stroke onset to be included in the SU group. The prespecified control group was comprised of all remaining diabetic patients, and additional comparisons were made specifically with those on no medication for DM and those on any non-SU medication for DM.

A secondary analysis was performed on the patients taking a SU before stroke onset to assess the effect of continued SU use. For this analysis, patients who continued SUs for ≥3 days after stroke onset were allocated to the treatment group. Patients who discontinued SUs on hospitalization were allocated to the control group.

Patients taking a first-generation SU (acetohexamide, chlorpropamide, tolbutamide, tolazamide, and carbutamide) were excluded from the analysis. Such drugs are rarely prescribed, and they are associated with higher incidences of drug–drug interactions, hypoglycemia, and other complications as compared with second- and third-generation drugs.11 Additionally, first-generation drugs have a much lower affinity for the SU receptor1,2 limiting their potential benefit in acute stroke.

Baseline patient characteristics, including age, sex, ethnicity, smoking status, history of stroke, transient ischemic attack, myocardial infarction, atrial fibrillation, ischemic heart disease, congestive heart failure, hypertension, and current medications (insulin, statin, aspirin, metformin), were extracted from the VISTA database. Patient characteristics pertaining to initial hospital presentation, including NIHSS score and blood glucose level, were also extracted. Finally, patient outcome data were extracted, including the mRS score at 30 and 90 days, NIHSS score at 90 days, and mortality at 90 days.

Our primary outcome measures were (1) baseline NIHSS score; and (2) 90-day mRS score. Generalized ordinal logistic regression models were used to compare these outcomes between patients with and without SU exposure, adjusting for age, sex, and race/ethnicity. Additionally, baseline NIHSS score was included as a stratification factor in the analyses after initial presentation, categorized as ≤10, 11 to 15, 16 to 20, or ≥21. For comparison with other studies, we also used the nonparametric Cochran-Mantel-Haenszel approach using modified ridit scores.13,14 We analyzed dichotomized 90-day mRS scores by comparing the proportion of patients with an mRS ≥2 at 90 days by SU exposure using logistic regression at the time of adjusting for age, sex, race/ethnicity, and baseline NIHSS score.

Secondary outcome measures were 30-day mRS score and NIHSS score at 90 days, which were analyzed with the same approaches as the primary outcomes.

Additionally, primary and secondary outcomes were compared between patients with any DM medication exposure and patients with no DM medication exposure.
associated with lower baseline NIHSS scores and trends toward better outcomes at 90 days (Table 4). The estimates of effect size were similar for SU, metformin, and insulin.

**Discussion**

The present study suggests that use of SU drugs before stroke onset does not influence long-term functional outcome among diabetic patients. Patients with prestroke SU use may have presented with less severe stroke compared with those on no medications for diabetes, but no sustained effect was observed nor was there a difference when compared with patients on any other diabetes medication. One previous report suggested a beneficial effect of SUs in a small cohort, but another similarly small study did not. The present study offers several methodological advantages over these prior observational studies. First, our results are derived from prospective trials with standardized assessments and meticulous data monitoring, providing extremely high-quality data.

### Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SU (n=298)</th>
<th>All Control Subjects (n=752)</th>
<th>Controls on Non-SU DM Medications (n=174)</th>
<th>Controls on No DM Medications (n=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>70.5 (9.5)</td>
<td>70.1 (10.9)</td>
<td>69.4 (11.4)</td>
<td>70.3 (10.7)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>165 (55%)</td>
<td>396 (53%)</td>
<td>84 (49%)</td>
<td>312 (54%)</td>
</tr>
<tr>
<td>Ethnicity, white</td>
<td>243 (82%)</td>
<td>616 (82%)</td>
<td>141 (81%)</td>
<td>475 (82%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>46 (15%)</td>
<td>177 (24%)†</td>
<td>27 (16%)</td>
<td>150 (26%)†</td>
</tr>
<tr>
<td>Baseline blood glucose level, mmol/L*</td>
<td>11.2 (4.6)</td>
<td>10.7 (4.3)</td>
<td>10.6 (4.1)</td>
<td>10.7 (4.4)</td>
</tr>
</tbody>
</table>

**History of**

- Hypertension: 243 (82%) 650 (87%)† 149 (86%) 501 (87%)†
- Prior stroke: 72 (27%) 194 (27%) 59 (34%) 135 (25%)
- TIA: 21 (7%) 82 (11%) 20 (12%) 62 (11%)
- Myocardial infarction: 47 (16%) 114 (15%) 26 (15%) 88 (15%)
- Atrial fibrillation: 72 (24%) 181 (24%) 45 (26%) 136 (24%)
- Ischemic heart disease: 100 (38%) 240 (37%) 74 (43%) 166 (35%)
- Congestive heart failure: 25 (11%) 58 (10%) 19 (12%) 35 (9%)

**Drug use prior to stroke**

- Insulin: 18 (6%) 87 (12%)† 87 (50%)† ... 87 (50%)† ...
- Metformin: 68 (23%) 80 (11%)† 80 (46%)† ...
- Statin: 31 (10%) 63 (8%) 19 (11%) 44 (8%)
- Aspirin: 58 (20%) 96 (13%)† 42 (24%) 54 (9%)†

All values are reported as no. (%) unless otherwise noted.
*Values are reported as mean (SD).
†In comparison to the SU group, P < 0.05 by χ² tests for dichotomous variables or t tests for continuous variables.
TIA indicates transient ischemic attack.

### Table 2. Stroke Severity and Outcomes Associated With Prestroke SU Use

<table>
<thead>
<tr>
<th></th>
<th>SU (n=298)</th>
<th>No DM Medications (n=578)</th>
<th>Non-SU DM Medications (n=174)</th>
<th>SU Versus All Control Subjects</th>
<th>SU Versus No DM Medications</th>
<th>SU Versus Non-SU DM Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission NIHSS</td>
<td>11 (8–16)</td>
<td>13 (6–18)</td>
<td>10 (8–16)</td>
<td>0.75 (0.59–0.97) 0.027 (0.30)</td>
<td>0.69 (0.53–0.89) 0.004 (0.07)</td>
<td>1.04 (0.73–1.48) 0.84 (0.88)</td>
</tr>
<tr>
<td>Outcome at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score</td>
<td>4 (2–5)</td>
<td>4 (3–5)</td>
<td>4 (2–5)</td>
<td>0.92 (0.72–1.18) 0.52 (0.80)</td>
<td>0.92 (0.71–1.20) 0.54 (0.75)</td>
<td>0.97 (0.68–1.37) 0.84 (0.66)</td>
</tr>
<tr>
<td>mRS &gt;2</td>
<td>70%</td>
<td>75%</td>
<td>71%</td>
<td>0.78 (0.55–1.10) 0.15</td>
<td>0.82 (0.58–1.18) 0.29</td>
<td>0.80 (0.50–1.30) 0.38</td>
</tr>
<tr>
<td>Outcome at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score</td>
<td>4 (1–5)</td>
<td>4 (2–5)</td>
<td>4 (1–5)</td>
<td>0.96 (0.76–1.23) 0.78 (0.40)</td>
<td>0.95 (0.74–1.23) 0.69 (0.20)</td>
<td>1.00 (0.71–1.40) 0.99 (0.85)</td>
</tr>
<tr>
<td>mRS &gt;2</td>
<td>63%</td>
<td>71%</td>
<td>60%</td>
<td>0.83 (0.60–1.15) 0.27</td>
<td>0.76 (0.55–1.07) 0.11</td>
<td>1.04 (0.67–1.62) 0.86</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>4 (1–9)</td>
<td>5 (2–12)</td>
<td>3 (1–6)</td>
<td>0.84 (0.62–1.13) 0.25 (0.72)</td>
<td>0.88 (0.65–1.19) 0.41 (0.33)</td>
<td>1.12 (0.73–1.73) 0.60 (0.37)</td>
</tr>
<tr>
<td>NIHSS &gt;1</td>
<td>78%</td>
<td>81%</td>
<td>74%</td>
<td>1.03 (0.72–1.45) 0.89</td>
<td>0.99 (0.68–1.43) 0.96</td>
<td>1.20 (0.76–1.89) 0.44</td>
</tr>
<tr>
<td>Mortality</td>
<td>22%</td>
<td>20%</td>
<td>20%</td>
<td>1.30 (0.92–1.86) 0.13</td>
<td>1.34 (0.93–1.94) 0.11</td>
<td>1.20 (0.72–2.00) 0.47</td>
</tr>
</tbody>
</table>

Values are reported as median (interquartile) for categorical variables or as percentage for dichotomized variables. All P values were calculated using ordinal logistic regression (and Cochran-Mantel-Haenszel test) for categorical variables or logistic regression for dichotomized variables. Analyses of baseline NIHSS were adjusted for age, sex, and race/ethnicity. Analyses of all outcomes at 30 and 90 days were also adjusted for baseline NIHSS. Note that higher ORs reflect worse outcomes for subjects on no DM medications compared with any DM medications.
and a substantially larger sample than both prior studies combined. This allowed us to demonstrate that SUs had no advantage over other commonly used DM medications. By comparing SUs with other agents, this study was better able to assess a class effect from any glucose-lowering agent. This is particularly relevant because patients who were on no medication fared worse than those on any DM medication such that a direct comparison of SUs with this completely untreated group could lead to erroneous conclusions about a specific effect of these agents. Additionally, our study examined widely accepted, clinically meaningful outcome measures, including the mRS at 90 days, which is commonly used in stroke trials, as well as the NIHSS and mortality at 90 days. Our results were also concordant across all outcomes, strengthening our conclusions.

As the first prospective study to address the effect of SU use on stroke severity and outcome, the current study provides important insights into this relationship; however, there are several limitations. A remarkable finding in our study was that patients not on medical therapy for DM had more severe strokes and had worse clinical outcomes when compared with those treated with any DM medication. This was also noted in the report by Kunte et al, and although our study confirms this result, there may be substantial confounding, particularly with regard to DM severity, duration of disease, or disease control. Diabetic patients who are treated with diet alone should theoretically have less severe DM than those who require medical therapy. One possible explanation for our finding is that those who are not on medical treatment had more poorly controlled DM and are not treated because of poor adherence, impaired access to care, and/or overall poor health. Another is that those patients on no medication had worse glycemic control in the early phase of their stroke, which contributed to worse outcome. In the current study, there was no significant difference between blood glucose levels on admission between groups, but a single random glucose level is not an adequate assessment of DM severity. Furthermore, few diabetic complications were specified at baseline in the VISTA database, precluding adjustment for this potential indicator of DM disease control. Given the well-established association between uncontrolled DM and increased stroke risk/severity, it seems likely that patients who were not on medical therapy had poorly controlled DM. Unfortunately, DM severity and duration cannot be directly addressed in this study or any of the previous studies of SU use in stroke. Future prospective studies looking at DM treatment and stroke outcome should incorporate measures of DM severity such as hemoglobin A1C and time since diagnosis of diabetes.

Figure 1. Baseline NIHSS score: (A) comparing those with SU use (n=298) versus those on no DM medications (n=578); (B) comparing those with SU use versus those on at least 1 non-SU DM medication (n=174). NIHSS scores were categorized as ≤10, 11 to 15, 16 to 20, or ≥21, representing 4 incremental levels of initial stroke severity.

Figure 2. Ninety-day mRS Score: (A) comparing those with SU use (n=298) versus those on no DM medications (n=578) at baseline; (B) comparing those with SU use versus those on at least 1 non-SU DM medication (n=174) at baseline. Brackets indicate the number of patients achieving a good mRS score of ≤2.
Table 3. Stroke Severity and Outcomes Comparing No DM Medication With Any DM Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>No DM Medication (n=578)</th>
<th>Any DM Medication (n=472)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission NIHSS</td>
<td>13 (6–18)</td>
<td>11 (8–16)</td>
<td>1.48 (1.18–1.86)</td>
<td>0.001 (0.006)</td>
</tr>
<tr>
<td>Outcome at 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score</td>
<td>4 (3–5)</td>
<td>4 (2–5)</td>
<td>1.10 (0.88–1.38)</td>
<td>0.41 (0.68)</td>
</tr>
<tr>
<td>mRS &gt;2</td>
<td>75%</td>
<td>68%</td>
<td>1.21 (0.88–1.66)</td>
<td>0.23</td>
</tr>
<tr>
<td>Outcome at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score</td>
<td>4 (2–5)</td>
<td>4 (1–5)</td>
<td>1.08 (0.87–1.35)</td>
<td>0.49 (0.36)</td>
</tr>
<tr>
<td>mRS &gt;2</td>
<td>71%</td>
<td>62%</td>
<td>1.31 (0.97–1.77)</td>
<td>0.076</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>5 (2–12)</td>
<td>3 (1–8)</td>
<td>1.34 (1.02–1.76)</td>
<td>0.035 (0.054)</td>
</tr>
<tr>
<td>NIHSS &gt;1</td>
<td>81%</td>
<td>77%</td>
<td>1.11 (0.81–1.53)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mortality</td>
<td>20%</td>
<td>21%</td>
<td>0.79 (0.57–1.09)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are reported as median (interquartile range) for categorical variables or as percentage for dichotomized variables. All P values were calculated using ordinal logistic regression (and Cochran-Mantel-Haenszel test) for categorical variables or logistic regression for dichotomized variables. Analyses of baseline NIHSS were adjusted for age, sex, and race/ethnicity. Analyses of all outcomes at 90 days were also adjusted for baseline NIHSS. Note that higher odds ratios reflect worse outcomes for subjects on each medication specified compared with no DM medication.

This study does not directly address whether SU agents are neuroprotective when given after stroke onset, as demonstrated in animal experiments. However, these drugs have long serum half-lives and prolonged systemic activity with serum glucose-lowering effects that last >24 hours. Exposure to such agents before stroke should permit reliable drug distribution and provide preischemic neuroprotection. During ischemia, vessel occlusion and impaired cerebral perfusion may prevent the drug from reaching tissue at risk, thus limiting its potential efficacy. It therefore seems unlikely that acute poststroke SU treatment would be beneficial if no effect is observed in patients who are pretreated. However, SU receptor 1 expression is elevated up to 8 hours after the onset of ischemia, and the ideal time window for SU-mediated neuroprotection remains unknown. Sustained drug exposure poststroke may be necessary to achieve clinically relevant neuroprotection. Kunte et al reported a benefit to SU use when administered both before stroke onset and during the hospital course, but they did not assess the impact of prestroke exposure alone and did not systematically or prospectively address long-term outcome. Weih et al noted that 57% of their treatment group (prior SU use) continued oral SU use during hospitalization, but this was not further addressed in the analysis. We attempted to address this in a secondary analysis of patients with prior plus continued SU use. No significant effect was observed, but only 28 patients (of 298 on a SU) continued use in the hospital, severely limiting the power of this subgroup analysis. We were also unable to address the impact of drug doses and other pharmacokinetic parameters in this study.

The current study also does not address the potential relevance of stroke subtype on the impact of SUs. The incidence of stroke subtypes differs between diabetics and nondiabetics. Stroke subtype has been shown to influence both functional outcome and survival. Furthermore, it was previously reported that only nonlacunar strokes significantly benefitted from SU use. It has been hypothesized that nonlacunar strokes may have greater benefit as a result of increased collaterals and improved cerebral blood flow with reduced edema. We had insufficient data regarding subtypes to address this issue, which may confound our results.

In summary, in a large prospective cohort, SU use before stroke onset did not affect functional outcome when compared with other DM treatments or with no treatment. However, patients who were not using any medication to control their DM presented with more severe strokes and experienced worse long-term outcomes than those on any DM treatment, which could reflect a general effect of DM drugs or differences between groups in DM severity, duration of disease, or stroke subtype. Future studies evaluating DM treatment and stroke are warranted to further characterize this relationship. Stroke studies in general should include reliable measures of DM severity and disease control in the analysis and account for possible differences in stroke subtype between groups.

Table 4. Stroke Severity and Outcomes Associated With Prestroke Metformin or Insulin Use

| | Metformin (n=148) | Insulin (n=105) | No DM Medications (n=578) | Metformin Versus No DM Medications | Insulin Versus No DM Medications |
| | OR (95% CI) | P | OR (95% CI) | P |
| Admission NIHSS | 10 (6–16) | 11 (7–16) | 13 (6–18) | 0.59 (0.42–0.83) | 0.003 | 0.67 (0.45–0.99) | 0.046 |
| Outcome at 90 days | | | | |
| mRS score | 3 (1–4) | 3 (1–5) | 4 (2–5) | 0.72 (0.51–1.00) | 0.06 | 0.84 (0.56–1.24) | 0.37 |
| mRS >2 | 58% | 56% | 71% | 0.66 (0.43–1.01) | 0.06 | 0.65 (0.40–1.05) | 0.08 |
| NIHSS score | 4 (1–10) | 4 (1–42) | 5 (2–12) | 0.57 (0.36–0.88) | 0.013 | 0.93 (0.58–1.50) | 0.78 |
| NIHSS >1 | 72% | 75% | 81% | 0.75 (0.47–1.17) | 0.20 | 0.87 (0.51–1.47) | 0.60 |
| Mortality | 15% | 23% | 20% | 0.85 (0.50–1.44) | 0.55 | 1.40 (0.82–2.38) | 0.21 |

Values are reported as median (interquartile range) for categorical variables or as percentage for dichotomized variables. All P values were calculated using ordinal logistic regression for categorical variables or logistic regression for dichotomized variables. Analyses of baseline NIHSS were adjusted for age, sex, and race/ethnicity. Analyses of all outcomes at 90 days were also adjusted for baseline NIHSS. Note that higher odds ratios reflect worse outcomes for subjects on each medication specified compared with no DM medications.
Acknowledgments
We thank all of the investigators, coordinators, and patients who contributed data to the Virtual International Stroke Trials Archive (VISTA).

Sources of Funding
C.G.F. and S.E.K. were supported by the Doris Duke Clinical Research Foundation.

Disclosures
None.

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Stroke. 2011;42:710-715; originally published online February 17, 2011;
doi: 10.1161/STRÖKEAHA.110.599274
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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