Preexisting Statin Use Is Associated With Greater Reperfusion in Hyperacute Ischemic Stroke

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Background and Purpose—Statin pretreatment has been associated with improved outcomes in patients with ischemic stroke. Although several mechanisms have been examined in animal models, few have been examined in patients. We hypothesized that patients using statins before stroke onset may have greater reperfusion than patients not using statins.

Methods—Acute ischemic stroke patients underwent 2 MR scans: within 4.5 (tp1) and at 6 hours (tp2) after stroke onset. Regions of reperfusion were defined by prolonged mean transit time (MTT) at tp1, which normalized at tp2. Four MTT thresholds were assessed to ensure that results were not spuriously based on an arbitrary threshold. Baseline characteristics, relative reperfusion, and change in NIHSS between tp1 and 1-month follow-up (ΔNIHSS) were compared between patients who were using statins at stroke onset and those who were not.

Results—Thirty-one stroke patients were prospectively enrolled; 12 were using statins and 19 were not. Baseline characteristics did not differ between the 2 groups except the statin group had greater coronary artery disease ($P=0.03$). Patients using statins showed significantly greater reperfusion compared to untreated patients across all MTT thresholds. For MTT of 4 seconds, median relative reperfusion was 50% (interquartile range, 30%–56%) in the preexisting statin group versus 13% (interquartile range, 5%–36%) in the untreated group ($P=0.014$). The statin group had greater ΔNIHSS (8.8±4.0 points) compared to the untreated group (4.4±5.7 points; $P=0.028$).

Conclusions—Statin use before ischemic stroke onset was associated with greater early reperfusion and NIHSS improvement. Further studies in larger populations are required to confirm our preliminary findings. (Stroke. 2011;42:1307-1313.)

Key Words: ischemic stroke ■ reperfusion ■ statin

3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) are widely prescribed for the prevention of vascular events. The Stroke Prevention with Aggressive Reduction of Cholesterol Level (SPARCL) trial demonstrated that atorvastatin reduced risk of recurrent stroke by 16% compared to placebo.1 In addition to having fewer events, patients using atorvastatin showed a trend toward improved neurological outcomes at 90 days after their stroke outcome event.2 Several additional studies have found that patients using statins at the time of stroke onset had improved outcomes and lower mortality than those who were not using statins.3–6 Moreover, withdrawal of statins in patients admitted for ischemic stroke has been associated with worse neurological outcomes, greater early neurological deterioration, and larger infarct sizes.7

Although the neuroprotective mechanisms of statins in ischemia have not been fully elucidated, several potential roles in animals and humans have been studied. In rodent models, statins have been shown to promote fibrinolysis, inhibit prothrombotic pathways, and limit infarct size.8–11 In models of ischemia-reperfusion, statins have protected multiple organ systems against reperfusion injury12,13 and have augmented cerebral blood flow secondary to upregulation of endothelial nitric oxide synthase,14 although such a cerebral blood flow effect was not reproduced in humans with atherosclerotic carotid occlusion.15 In other clinical studies, statin use was associated with greater recanalization in a cohort of ischemic stroke patients undergoing acute intervention;16 in aneurysmal subarachnoid hemorrhage, patients treated with statins were less likely to have vasospasm.
develop. In several studies, the neuroprotective effects have been independent of cholesterol lowering. Given the potential vascular effects of statins in the setting of ischemia, we hypothesized that improved neurological outcomes observed with statin pretreatment may be related to greater reperfusion during the hyperacute phase of ischemic stroke. Thus, we measured early reperfusion (within 6 hours of stroke onset) in acute ischemic stroke patients, comparing patients with preexisting statin use to untreated patients.

**Patients and Methods**

**Patients and Inclusion Criteria**

This was a retrospective analysis of data from a prospectively collected observational study of serial MRIs performed in acute ischemic stroke patients at a large urban tertiary care referral center, admitting >800 ischemic strokes per year. Data from the first 31 patients in this study (with planned enrollment of 75 patients) were used for a retrospective analysis of the effect of statins on reperfusion. After Institutional Review Board approval, the study enrolled consecutive patients within 4.5 hours of stroke onset based on the following prespecified inclusion criteria: clinically suspected acute cortical ischemic stroke; age 18 years or older; NIHSS score ≥3; and patient or patient’s next of kin capable of informed consent. Exclusion criteria included bilateral strokes or any acute endovascular or surgical intervention. Both tissue plasminogen activator (tPA)-treated and untreated patients were included. For patients receiving tPA, the study imposed no delay in time to tPA treatment and no deviation from standard practices. The NIHSS was collected prospectively by a stroke neurologist on admission, at both imaging time points, and at 1 month follow-up. Clinical data including demographic data, medical history, and home medications were obtained by the research coordinator prospectively during enrollment.

**MRI Protocol**

Patients were scanned with MRI within 4.5 hours (tp1) and at 6 hours (tp2) after stroke onset on a 3-T Siemens whole-body Trio system with a circular polarized head coil. For patients receiving tPA, the tp1 scan was performed as soon as possible after tPA bolus. The protocol included diffusion-weighted images, fluid-attenuated inversion recovery images (repetition time/echo time = 10 000/115 ms; inversion time = 2500 ms; matrix = 512×416; 20 slices, slice thickness = 5 mm), and dynamic susceptibility contrast perfusion images with Gadolinium contrast injected at 5 mL/s with a power injector (a T2*-weighted gradient-echo planar imaging (EPI) sequence; TR (repetition time)/TE (echo time) = 1500/43 ms; 14 slices, slice thickness = 5 mm, zero interslice gap; matrix = 128×128). MRA was not performed.

**Data Analysis**

Mean transit time (MTT; [MTT = cerebral blood volume/cerebral blood flow]18) was chosen to define the perfusion deficit because MTT is uniform across gray and white matter (unlike cerebral blood flow or cerebral blood volume), allowing for use of a single threshold across both tissue types. Voxels within the middle cerebral artery (MCA) territory of the contralateral hemisphere were manually chosen to obtain an arterial input function. Six parameter rigid image registration was performed to align all images across both scans for each patient using FSL 3.2 (FMRIB). Accuracy of image registration was evaluated manually. MTT prolongation for each voxel within the ischemic hemisphere was calculated as: [MTT of ischemic voxel] – [median MTT of contralateral hemisphere]. A voxel was defined as “prolonged” if MTT was more than or equal to a predefined threshold. Because the perfusion deficit volume varies depending on the MTT threshold chosen, 4 MTT prolongation thresholds (3, 4, 5, and 6 seconds) were tested to determine if results were consistent across a range of putative thresholds. Prolonged MTT volumes provided measures of perfusion deficit volumes at tp1 and tp2. The absolute volume of reperfusion was calculated as: [prolonged MTT volume at tp1]–[prolonged MTT volume at tp2]. Subsequently, the relative volume of reperfusion was calculated as: [prolonged MTT at tp1 – prolonged MTT at tp2]/[prolonged MTT at tp1] (Figure 1). The individuals performing the reperfusion calculations were blinded to the treatment status of the patient. Isolated regions of abnormal perfusion <1 mL were removed from the analysis to minimize inclusion of misregistered regions or noise-induced variations.

**Statistical Analysis**

Preexisting statin use and untreated groups were compared using the Wilcoxon rank sum test for continuous variables except when data were Gaussian (confirmed by the Kolmogorov-Smirnov and D’Agostino-Pearson omnibus tests), when the t test was used. Fisher exact test compared categorical baseline characteristics between the 2 groups. Alpha ≤0.05 was required for statistical significance. Statistical analyses were performed using STATA 10.1.

**Statins and Relative Reperfusion**

Relative reperfusion for each MTT threshold (3, 4, 5, and 6 seconds) was compared between the untreated and statin groups. In addition to the total group, the tPA-treated subgroup was analyzed to ensure that statin effects were not confounded by the higher proportion of statin patients receiving tPA. A linear regression model was developed as a prediction model for relative reperfusion based on the MTT of 4-second threshold (because this is a commonly used threshold of ischemia in acute stroke literature). Predictors were selected with a forward stepwise procedure in which P=0.20 was required for entry and P≤0.05 was required to be retained in the model. At each step, regression diagnostics evaluated distributional assumptions of the residuals and functional form of the covariates. Ten potential covariates were considered: preexisting statin use; tPA treatment; volume of tp1 perfusion deficit (MTT = 4 seconds); age; gender; admission NIHSS score; admission mean arterial pressure; admission glucose; low-density lipoprotein; and time between tp1 and tp2 scans. Diffusion-weighted imaging volume at tp1 was considered for inclusion in the model; however, diffusion-weighted imaging volume demonstrated strong covariance (r=0.74; P<0.0001) with volume of tp1 perfusion deficit, leading to multicollinearity. Therefore, we chose to include only volume of tp1 perfusion deficit in the model to control for baseline volume of initial ischemia. Model goodness-of-fit was assessed by Akaike information criterion. Potential interactions between statin use and tPA treatment or mean arterial pressure were assessed.

**Statins and Neurological Improvement**

Neurological improvement, as assessed by ΔNIHSS (NIHSS on admission–NIHSS at 1 month), was compared in the untreated and preexisting statin use groups. This comparison was performed in all patients and in the tPA-treated subgroup. In the same way as described for relative reperfusion, a forward stepwise procedure for a linear regression model was created to identify which of 10 baseline clinical variables predicted neurological improvement as measured by ΔNIHSS. Potential interactions between statin use and tPA treatment or age were assessed.

**Results**

Of 31 acute ischemic stroke patients enrolled, 12 were using statins at stroke onset and 19 were not. Patient demographics and baseline characteristics were not significantly different between the 2 groups except that the statin group had significantly more patients with a history of coronary artery disease (P=0.03). Patients were imaged with MRI at 3.0±0.8 hours (tp1) and 6.4±0.4 hours (tp2) after onset. The coregistered images were well-aligned with the template images, yielding inaccuracies <3 voxels in any direction. To assess whether the location of perfusion deficit territories were
Relative Reperfusion = Absolute Reperfusion / Prolonged MTT tp1

Figure 1. Calculation of relative reperfusion. Mean transit time (MTT) maps were prepared for each time point. For each MTT threshold, all voxels with values more than the chosen MTT threshold were defined as “prolonged.” Prolonged MTT volumes provided a measure of the perfusion deficit volume at <4.5 hours (tp1) and at 6 hours (tp2). Absolute and relative reperfusion volumes were calculated as shown. Warm colors represent maximal hypoperfusion with longer MTT and cool colors represent no hypoperfusion with short MTT, as shown on the color bar. The orange outline delineates a perfusion deficit defined by an MTT threshold >4 seconds longer than the median MTT of the contralateral hemisphere. At tp2, the perfusion deficit shrinks; thus, the white outline delineates regions of reperfusion using this threshold (>4 seconds).

balanced between the untreated and preexisting statin use groups, perfusion deficit territories based on tp1 MTT maps were assigned to 1 of 4 groups: (1) internal carotid artery; (2) complete MCA; (3) partial MCA; and (4) small MCA (Figure 2). There were no significant differences between the 2 groups.

To assess how representative our study population (N=31) was relative to our hospital stroke population (N=2057) over the 2.5-year enrollment time period, we compared characteristics of both groups. Whereas age, gender, and race were similar, the mean NIHSS score was higher in the study cohort for non-tPA-treated patients. In addition, for tPA-treated patients, the mean door-to-needle time in the study cohort was shorter compared to that of the hospital tPA-treated patients (51 versus 60 minutes; \(P=0.04\)). There was no difference in rate of symptomatic intracerebral hemorrhage (Supplemental data, http://stroke.ahajournals.org).

Statin Use Is Associated With Increased Relative Reperfusion

We compared relative reperfusion in the untreated group and statin group for each of four MTT thresholds to determine if findings were consistent across all MTT thresholds. Relative reperfusion was greater in the statin group compared with the untreated group for all MTT thresholds (Figure 3A). Median reperfusion across the 4 MTT thresholds for the statin group was 48% (IQR, 28%–64%), and for the untreated group it was 13% (IQR, 4%–35%).

Because tPA treatment was more common in the statin group, we performed the same analysis in the subset of 23 patients treated with tPA to determine if the statin effect persisted in this subgroup. We continued to observe greater relative reperfusion in the statin group in 3 of the 4 MTT thresholds, with a strong trend for MTT of 3 seconds (Figure 3B). For tPA-treated patients, median reperfusion across the 4 MTT thresholds for the statin group was 48% (IQR, 26%–56%), and for the untreated group it was 15% (IQR, 2%–30%).

A forward selection stepwise procedure determined which clinical variables best predicted early reperfusion after stroke. In addition to statin use, 9 baseline variables that were hypothesized to possibly affect reperfusion were included (Table 1, top 9 variables). Clinical variables that remained in the final model included: (1) statin use, \(\beta (SE)=17.9 (7.3) (P=0.021)\); (2) volume t1 perfusion deficit, \(\beta (SE)=-0.156 (0.06) (P=0.024)\); and (3) admission mean arterial pressure, \(\beta (SE)=-0.318 (0.15) (P=0.040)\). The final model explained 41.1% of the variance in relative reperfusion (Table 2). Therefore, at stroke onset, statin use, smaller perfusion deficit, and lower blood pressure were the best predictors of relative reperfusion.

Statin Use Predicts NIHSS Improvement

After assessing variables associated with reperfusion, we evaluated how preexisting statin use may predict neurological improvement defined by the absolute change in NIHSS from admission to 1 month follow-up (ΔNIHSS). The ΔNIHSS was greater in the statin group at 8.8±4.0 (mean±SD) points compared to the untreated group at 4.4±5.7 points (\(P=0.028\); Figure 4A). When, the tPA-treated subgroup (n=23) was evaluated in a separate analysis, ΔNIHSS continued to be greater in patients using statins at stroke onset at 8.9±4.2 points compared to those who were not at 4.4±4.9 points (\(P=0.048\); Figure 4B).

A forward selection stepwise procedure was utilized to develop a prediction model of ΔNIHSS. Clinical variables that remained in the final model included: (1) preexisting statin use, \(\beta (SE)=4.82 (1.7) (P=0.010)\) and (2) age, \(\beta\)
In this model, statin use and younger age were associated with NIHSS improvement, together explaining 31.9% of the variance in NIHSS (Table 2).

Discussion

Statins and Early Reperfusion

In this retrospective study of prospectively collected MRI data, patients using statins before stroke onset had 2- to 3-fold greater early reperfusion than patients not using statins. This difference persisted across all MTT thresholds examined, indicating that regardless of how the perfusion deficit was defined (conservatively or liberally), statin use was associated with greater reperfusion. Given the increased frequency of tPA treatment in the statin group, we analyzed this group separately and found that statin use continued to be associated with greater relative reperfusion.

Based on vasculoprotective effects of statins, we hypothesized that early reperfusion may be responsible, in part, for the improved clinical outcomes seen in statin-pretreated populations in large clinical trials. Regardless of statin type, animal studies have found decreased infarct size with statin pretreatment; however, pathways underlying this neuroprotection continue to be investigated. Potential mechanisms leading to early reperfusion fall into 3 broad categories: (1) improved blood flow/vasomotor reactivity; (2) antithrombotic effects; and (3) anti-inflammatory effects. Before cholesterol-lowering properties take effect, statins exert pleiotropic effects on the vascular wall, including the upregulation of endothelial nitric oxide synthase, increasing nitric oxide production with resultant increased cerebral blood flow. Consistent with this mechanism, statins decreased perfusion deficits after rodent MCA occlusion and improved cerebral vasomotor reactivity in stroke patients undergoing SPECT imaging. The antithrombotic effects of statins act via increasing endogenous tPA levels as well as by inhibiting plasminogen activator. Moreover, increased nitric oxide leads to decreased platelet activation and aggregation. Finally, the anti-inflammatory effect of statins was...
Statins and Neurological Improvement

Preexisting statin use predicted greater neurological improvement as measured by ΔNIHSS in the entire sample as well as in tPA-treated patients. In a multivariable model, besides statin use, younger age also predicted improved neurological status, a finding that was not surprising because age is one of the strongest predictors of disability after stroke.40,41

Our finding that statin pretreatment was associated with greater neurological improvement in NIHSS may be consistent with findings from several large clinical studies that found improved clinical outcomes in statin-pretreated patients.2–6 Besides vasculoprotective effects, statins have been reported to stimulate production of antiapoptotic protein, Bcl-2, in neurons and human neuroblastoma cells42,43 and to prevent glutamate-induced excitotoxicity in cortical neurons.44 Statins administered within 1 day of stroke were found and accordingly may prevent “no-reflow,” a phenomenon in which tissue reperfusion does not occur despite vessel recanalization.30,31

In a linear regression model, we identified 3 baseline variables that explained 41% of the variance in relative reperfusion: statin use, perfusion deficit volume at tp1, and baseline mean arterial pressure. Our data suggest that larger perfusion deficits have relatively less reperfusion, a finding supported by a recent report in a smaller cohort of tPA-treated patients.32 A smaller initial perfusion deficit may signify less clot burden, facilitating recanalization either spontaneously or in the presence of thrombolytics. Clinical studies demonstrated that larger perfusion lesions, baseline stroke severity, and large-vessel occlusion predicted infarct growth, stroke evolution, and early neurological deterioration.33,34

Our model revealed that higher blood pressure (BP) was significantly associated with less reperfusion. Whereas several observational studies have associated elevated BP early after stroke onset with increased disability, several of these studies, including the International Stroke Trial, found a U-shaped curve in which low BP was also associated with poor outcomes.35 Moreover, this negative relationship of BP and reperfusion opposes a common approach of stroke physicians to avoid BP-lowering, especially in chronically hypertensive patients. In our sample, 3 (of 7) patients did not receive tPA because of elevated BP, suggesting the possibility of less reperfusion attributable to no tPA treatment; however, tPA was not a significant predictor of reperfusion in our sample and, thus, the relationship between BP and reperfusion warrants further study.

We chose to use reperfusion determined by MTT as an outcome measure rather than recanalization (using MRA) because reperfusion is a more sensitive and quantitative measure than recanalization, which relies on crude measures of stenosis. Studies have shown that recanalization may occur without tissue reperfusion because of proximal clot breakdown with distal embolization, and reperfusion may occur in the absence of recanalization likely attributable to collateral flow.36–38 Moreover, a recent study comparing CT perfusion to CTA suggested that reperfusion more accurately predicted infarct volumes than recanalization.39

Table 2. Multivariable Model of Clinical Variables Predicting Relative Reperfusion and Change in National Institutes of Health Stroke Scale

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>β (SE)†</th>
<th>P‡</th>
</tr>
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<tbody>
<tr>
<td>Predictors of relative reperfusion*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexisting statin use</td>
<td>17.9 (7.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>Volume prolonged MTT at tp1</td>
<td>−0.156 (0.06)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>−0.318 (0.15)</td>
<td>0.040</td>
</tr>
<tr>
<td>Predictors of ΔNIHSS from admission to 1 month§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexisting statin use</td>
<td>4.82 (1.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>Age</td>
<td>−0.163 (0.06)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

MTT indicates mean transit time; NIHSS, National Institutes of Health Stroke Scale; ΔNIHSS, change in National Institutes of Health Stroke Scale score; SE, standard error.

*Model including preexisting statin use, volume of prolonged MTT at tp1, and admission mean arterial pressure explained 41.1% of the variance in relative reperfusion.
†β (SE)=regression coefficient (standard error).
‡P<0.05 was considered statistically significant.
§Model including the preexisting statin use and age explained 31.9% of the variance in ΔNIHSS.

Figure 4. Statin use and neurological improvement. A. Entire sample, n=31. Box plots (median, interquartile range) for improvement in National Institutes of Health Stroke Scale (NIHSS) score from admission to 1-month follow-up (ΔNIHSS) are shown for all 31 patients. There was greater NIHSS score improvement in the statin group compared to the untreated group. B. Tissue plasminogen activator (tPA)-treated patients only, n=23. Box plots for ΔNIHSS are shown for tPA-treated patients only. There was significantly greater improvement in NIHSS score in the statin group.

Bcl-2, in neurons and human neuroblastoma cells42,43 and to prevent glutamate-induced excitotoxicity in cortical neurons.44 Statins administered within 1 day of stroke were found...
to improve synaptogenesis, neurogenesis, and angiogenesis in a rodent MCA occlusion model.\textsuperscript{45}

Our study has several limitations. Limited sample size may result in type II errors because of insufficient power. Although the study was prospective, there was no randomization of treatment, which may lead to selection bias. The treatment groups were unblinded; however, the investigators performing the reperfusion analysis were blinded to the clinical data. We obtained information on statin use from patients and family without independent confirmation. Patients using statins received more tPA than the untreated patients (though not statistically significant), so we performed the analysis in the tPA-treated subgroup to eliminate tPA as an independent variable and found similar results. Ideally, the study would be repeated with a larger sample of non-tPA-treated patients. We identified greater coronary artery disease in the statin group, as might be expected because coronary artery disease is a major indication for statin use. This imbalance may have introduced bias favoring reperfusion attributable to better medical care before stroke onset or limiting reperfusion because of greater medical comorbidities in coronary artery disease patients. Our study cohort included strokes of greater severity compared to the hospital stroke patients admitted to our institution; therefore, our results cannot be directly applied to patients with low stroke severity. Furthermore, our study did not include MRA, which would have given information about site of occlusion and degree of recanalization. However, by evaluating the location of the tPA perfusion deficit territories, we did not find any significant imbalance between the 2 groups (Figure 2), suggesting that bias attributable to unequal distribution of occlusion sites is less likely.

Conclusions
Preexisting statin use was associated with greater reperfusion and neurological improvement, raising the hypothesis that statin pretreatment may improve clinical outcomes after stroke by enhancing early reperfusion. Because of the small patient sample with nonrandomized treatment, further studies are required to confirm these findings.

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Disclosures
None.

References


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SUPPLEMENTAL MATERIAL

Supplemental Methods

To assess how representative our study population (N=31) was relative to our hospital stroke population (N=2057) over the 2.5 year enrollment time period, we compared baseline characteristics of both groups (Table). Wilcoxon rank sum test was utilized for group comparisons of continuous variables (age, NIHSS, and door-to-needle time). Fisher’s exact test was utilized for group comparisons of binary variables (gender, race, and symptomatic hemorrhage rate).

Supplemental Table. Baseline Characteristics, Door-to-needle time, and symptomatic intracerebral hemorrhage (ICH) rate comparing the Study Cohort to the Hospital Population.

<table>
<thead>
<tr>
<th></th>
<th>tPA-treated 1/1/08-5/31/10</th>
<th>Non-tPA-treated 1/1/08-5/31/10</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Study Cohort N=23</td>
<td>Hospital Population N=120</td>
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<tr>
<td>Age (years), mean±SD</td>
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<td>65±17</td>
</tr>
<tr>
<td>NIHSS (points), mean±SD</td>
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<td>12±7</td>
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<tr>
<td>Female (%)</td>
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<td>51</td>
</tr>
<tr>
<td>Black (%)</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Door-to-needle time (min), mean±SD</td>
<td>51±14</td>
<td>60±18*</td>
</tr>
<tr>
<td>Symptomatic ICH Rate (%)</td>
<td>4.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*p< 0.05 for significant difference between the Study Cohort and the Hospital Population.

Supplemental References.

None.