Carotid Atherosclerosis and Prospective Risk of Dementia

Carrington R. Wendell, PhD; Shari R. Waldstein, PhD; Luigi Ferrucci, MD, PhD; Richard J. O’Brien, MD, PhD; James B. Strait, MD, PhD; Alan B. Zonderman, PhD

Background and Purpose—Although vascular risk factors have been implicated in the development of all-cause dementia and Alzheimer disease (AD), few studies have examined the association between subclinical atherosclerosis and prospective risk of dementia.

Methods—Participants from the Baltimore Longitudinal Study of Aging (n=364; age, 60–95 years; median age, 73; 60% male; 82% white) underwent initial carotid atherosclerosis assessment and subsequently were assessed for dementia and AD annually for up to 14 years (median, 7.0). Cox proportional hazards models predicting all-cause dementia and AD were adjusted for sex, age, race, education, blood pressure, cholesterol, cardiovascular disease, diabetes mellitus, and smoking.

Results—Sixty participants developed dementia, with 53 diagnosed as AD. Raw rates of future dementia and AD among individuals initially in the upper quintile of carotid intimal medial thickness or with bilateral carotid plaque were generally double the rates of individuals with intimal medial thickness in the lower quintiles or no plaque at baseline. Adjusted proportional hazards models revealed >2.5-fold increased risk of dementia and AD among individuals in the upper quintile of carotid intimal medial thickness, and approximately 2.0-fold increased risk of dementia among individuals with bilateral plaque.

Conclusions—Multiple measures of carotid atherosclerosis are associated with prospective risk of dementia. Individuals in the upper quintile of carotid intimal medial thickness or bilateral carotid plaque were at greatest risk. These findings underscore the possibility that early intervention to reduce atherosclerosis may help delay or prevent onset of dementia and AD. (Stroke. 2012;43:3319-3324.)

Key Words: Alzheimer disease ■ atherosclerosis ■ dementia ■ intimal medial thickness

The worldwide prevalence of dementia is expected to nearly double by 2030 and triple by 2050,1 and the search for risk and protective factors has consequently intensified. Historically, cardiovascular health was thought to contribute primarily to vascular dementia, although vascular diseases and risk factors are now understood to be related to all-cause dementia and Alzheimer disease (AD) as well.2 Cerebrovascular disease and cerebral hypoperfusion are considered likely mechanisms.3,4 Despite these new insights, there is relatively limited research investigating associations between subclinical, or presymptomatic, atherosclerosis and dementia.

Subclinical atherosclerosis is most commonly studied in the carotid arteries using ultrasonography. Cross-sectionally, increased prevalence of carotid atherosclerosis has been noted in several samples of patients with dementia and AD.5,6 Multiple indices of carotid atherosclerosis, including intimal medial thickness (IMT), plaque, and stenosis, also have been linked with accelerated cognitive decline among patients with AD3,5 and dementia-free individuals.9 Yet, studies examining the association between carotid atherosclerosis and incident dementia are sparse.

In the Cardiovascular Health Study, the highest quartile of carotid IMT was associated with a significantly increased risk of dementia and AD during a 5-year follow-up.10 Similarly, over a median follow-up of 9 years, the highest quintile of carotid IMT was related to prospective dementia and AD risk among Rotterdam Study participants.11 During shorter-term follow-up in the same study, carotid IMT risk ratios increased considerably, and carotid plaque was additionally associated with dementia outcomes.

More prospective research is needed to replicate and extend findings regarding incident dementia. Previous research has not consistently examined carotid plaque, an important indicator of degree of atherosclerosis progression. Further, the role of mild cognitive impairment (MCI), a frequent precursor to dementia, has been addressed inconsistently. Here, we examined the association between baseline carotid atherosclerosis, as measured by IMT and plaque, and prospective risk for all-cause dementia and AD among older
adults enrolled in the Baltimore Longitudinal Study of Aging (BLSA). We conducted analyses with inclusion and exclusion of MCI cases.

Subjects and Methods

Participants

Participants were enrolled in the BLSA, a prospective study of community-dwelling volunteers initiated by the National Institute on Aging in 1958. Approximately every 2 years, participants undergo medical, psychological, and cognitive testing. Beginning in 1994, carotid ultrasonography was performed on a BLSA subset as a function of sonographer availability (random with respect to participant scheduling and participant willingness to participate). No exclusion criteria were applied, and this subsample was representative of the overall BLSA sample. Participants were included in the present analyses if they underwent carotid ultrasonography at or after age 60 (hereafter referred to as baseline visit) and were cognitively normal. A total of 364 participants were available for the present analysis. Participants were followed annually for up to 14 years (mean, 6.7; SD, 3.5; median, 7.0) with comprehensive cognitive evaluations. No participants underwent carotid artery intervention during the study. All participants provided written informed consent. Institutional Review Board approval was obtained from Johns Hopkins Bayview Medical Center before 2002 and from MedStar Research Institute afterward.

Atherosclerosis Assessment

High-resolution B-mode ultrasonography of the common carotid arteries was performed with a linear-array, 5- to 10-MHz transducer (Ultramark 9 HDI; Advanced Technology Laboratories). A region 1.5 cm proximal to the carotid bifurcation was identified, and IMT of the far arterial wall was evaluated as the distance between the lumen/intimal interface and medial/adventitial interface. Specific care was taken to measure IMT in areas devoid of plaque. IMT was measured on a frozen-frame image, magnified to achieve higher resolution of detail, at 5 contiguous sites at 1-mm intervals in both common carotid arteries. The mean of these values and a dichotomy based on the 80th percentile of IMT (eg, 0.9 mm) were constructed to assess risk of development of dementia associated with carotid IMT and plaque, controlling for age, sex, race, education, systolic blood pressure, diastolic blood pressure, total and high-density lipoprotein cholesterol, cardiovascular disease, diabetes mellitus, and smoking. ApoE genotype was not included in the primary analyses because of insufficient data, although supplementary analyses were conducted in a subset of participants. Mean carotid IMT was examined continuously and dichotomously (≥80th percentile). Carotid plaques were analyzed by category (none, unilateral, bilateral), using no plaques as the reference category. The dependent measure was age at onset of dementia (all-cause or AD) or the last follow-up for those without dementia. Covariates of interest included levels of carotid IMT and plaque. Cox proportional hazards models were constructed to assess risk of development of dementia associated with carotid IMT and plaque, controlling for age, sex, race, education, systolic blood pressure, diastolic blood pressure, and high-density lipoprotein cholesterol, cardiovascular disease, diabetes mellitus, and smoking. ApoE genotype was determined by polymerase chain reaction amplification of leukocyte DNA, followed by HhaI digestion and product characterization and by TaqMan assay systems relying on several single-nucleotide polymorphisms around the ApoE gene. Participants were classified by presence vs absence of at least 1 ApoE e4 allele.

Statistical Analyses

Statistical analyses were performed using SAS version 9.2. Descriptive statistics and χ² tests were computed to examine sample characteristics, including rates of dementia across levels of carotid atherosclerosis. Kaplan-Meier survival curves and log-rank tests were generated to compare unadjusted patterns of survival across different levels of carotid IMT and plaque. Cox proportional hazards models were constructed to assess risk of development of dementia associated with carotid IMT and plaque, controlling for age, sex, race, education, systolic blood pressure, diastolic blood pressure, total and high-density lipoprotein cholesterol, cardiovascular disease, diabetes mellitus, and smoking. ApoE genotype was not included in the primary analyses because of insufficient data, although supplementary analyses were conducted in a subset of participants. Mean carotid IMT was examined continuously and dichotomously (≥80th percentile). Carotid plaques were analyzed by category (none, unilateral, bilateral), using no plaques as the reference category. The dependent measure was age at onset of dementia (all-cause or AD) or the last observed (censored) age of participants without diagnoses. Because of known associations among atherosclerosis, stroke, and dementia, analyses also were performed excluding all prevalent and incident stroke (assessed by history). Post hoc power analyses were performed using R version 2.15.0.

Results

Table 1 shows sample characteristics at first assessment. Participants ranged in age from 60 to 95 (mean, 73.6) and were 60.2% male, 81.9% white, 14.3% black, and 3.8% Asian, Pacific-Islander, American Indian, or other. The average participant was well-educated, with the equivalent of a Bachelor’s degree (ie, >16 years of education). There was a wide range of carotid IMT values (0.35–1.25 mm), and the majority of the sample had neither no (44.0%) or bilateral (41.5%) plaque. Twenty-three participants (6.3%) underwent carotid ultrasound and cognitive evaluation at first visit but did not undergo subsequent cognitive evaluation. During up to 14 years of follow-up, 60 cases of dementia were identified, of which 53 cases were AD. Of the overall sample (n=364), 47 individuals (12.9%) were diagnosed with MCI and 35 individuals (9.6%) had either history of stroke before baseline or incident stroke during the course of follow-up. Sample sizes
Table 1. Baseline Characteristics of Study Sample (n=364)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD) or %</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>73.6 (8.3)</td>
<td>60–95</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>60.2</td>
<td></td>
</tr>
<tr>
<td>Race (% white)</td>
<td>81.9</td>
<td></td>
</tr>
<tr>
<td>Education (y)</td>
<td>16.6 (2.7)</td>
<td>7–22</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.6 (18.1)</td>
<td>90–207</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>86.3 (10.1)</td>
<td>42–116</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.3 (38.4)</td>
<td>104–418</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dL)</td>
<td>112.4 (32.0)</td>
<td>45–291</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.0 (14.0)</td>
<td>21–111</td>
</tr>
<tr>
<td>Cardiovascular disease† (%)</td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering medication use (%)</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>55.8</td>
<td></td>
</tr>
<tr>
<td>Mean intimal medial thickness (mm)</td>
<td>0.63 (0.15)</td>
<td>0.35–1.25</td>
</tr>
<tr>
<td>IMT ≥0.80 mm (%)</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>Carotid plaques‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>Unilateral (%)</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Bilateral (%)</td>
<td>41.5</td>
<td></td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; HDL, high-density lipoprotein; IMT indicates intimal medial thickness; SBP, systolic blood pressure; SD, standard deviation. *Mean age at final follow-up visit was 80.3 y (SD=7.7); range, 61–96. †Cardiovascular disease included history of coronary artery disease, myocardial infarction, and heart failure. ‡n=357 for carotid plaque analyses.

Table 2. Dementia Incidence by Level of Atherosclerosis

<table>
<thead>
<tr>
<th>Atherosclerosis Measure</th>
<th>Dementia Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Dementia</td>
</tr>
<tr>
<td></td>
<td>(Stoke Excluded)</td>
</tr>
<tr>
<td>Mean IMT (n=364)*</td>
<td></td>
</tr>
<tr>
<td>&lt;0.80 mm</td>
<td>14.0</td>
</tr>
<tr>
<td>≥0.80 mm</td>
<td>28.1</td>
</tr>
<tr>
<td>Plaque (n=357)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10.2</td>
</tr>
<tr>
<td>Unilateral</td>
<td>13.5</td>
</tr>
<tr>
<td>Bilateral</td>
<td>22.3</td>
</tr>
</tbody>
</table>

MCI excluded

- Mean IMT (n=317)
  - <0.80 mm: 15.9, 14.3, 15.9, 14.2
  - ≥0.80 mm: 34.0, 31.4, 31.1, 27.9

Plaque (n=310)

- None: 11.6, 11.6, 12.0, 12.0
- Unilateral: 16.3, 14.3, 13.2, 10.8
- Bilateral: 25.6, 21.3, 24.1, 19.8

IMT indicates intimal medial thickness; MCI, mild cognitive impairment. *Sample sizes for all-cause dementia column only.

for analyses involving carotid plaque were slightly smaller (n_dementia=357, n_MCI=349) because of missing data.

Table 2 demonstrates increasing incidence rates of dementia and AD with increasing levels of carotid atherosclerosis. Regarding IMT, 14.0% of individuals with baseline carotid IMT <0.80 mm developed dementia during follow-up, whereas 28.1% of individuals with carotid IMT ≥0.80 mm developed dementia (χ²[1, n=364]=7.64, P=0.006). Rates were similar for AD (12.5% and 25.8%, respectively; [χ²(1, n=357)=7.13; P=0.008]) and after excluding stroke. Rates became more divergent after exclusion of MCI cases: 15.9% vs 34.0% for low compared with high IMT, respectively (χ²[1, n=317]=9.37; P=0.002), for all-cause dementia, and 14.3% vs 31.4% for low vs high IMT, respectively (χ²[1, n=310]=8.78; P=0.003), for AD. Regarding plaque, individuals with no, unilateral, and bilateral plaque demonstrated increasing rates of dementia (eg, 10.2%, 13.5%, and 22.3%, respectively) for all-cause dementia (χ²[2, n=357]=8.67; P=0.013).

The Figure shows unadjusted Kaplan-Meier survival curves of incident dementia across different levels of carotid IMT and plaque in the total sample. Similar patterns were noted for other subsamples (ie, AD, MCI excluded, stroke excluded). Log-rank tests did not show significant differences in median probability of dementia for either carotid IMT (P=0.779) or plaque, although the latter finding was marginal (P=0.059). Cox proportional hazards models demonstrated that carotid IMT was associated with an increased risk for dementia and AD (Table 3). Models with IMT coded continuously showed strong patterns of significance. Specifically, IMT indicates intimal medial thickness; MCI, mild cognitive impairment. *Sample sizes for all-cause dementia column only.

Figure. Kaplan-Meier survival curves of incident all-cause dementia by level of (A) carotid IMT and (B) carotid plaque. Statistical tests indicated the proportional-hazards assumption was not violated (A: χ²[12]=8.92; P=0.709; B: χ²[13]=6.76, P=0.914). For numbers of participants and diagnoses at each time point (online-only Data Supplement), IMT indicates intimal medial thickness.
Table 3. Association Between Baseline Carotid Atherosclerosis and Prospective Risk of Dementia

<table>
<thead>
<tr>
<th>Measure of Atherosclerosis</th>
<th>All-Cause Dementia</th>
<th>Alzheimer Disease</th>
<th>All-Cause Dementia (Stroke Excluded)</th>
<th>Alzheimer Disease (Stroke Excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.08 (0.88–1.32), P=0.475</td>
<td>1.09 (0.88–1.35), P=0.450</td>
<td>0.99 (0.79–1.25), P=0.960</td>
<td>1.00 (0.78–1.27), P=0.969</td>
</tr>
<tr>
<td>Dichotomous†</td>
<td>2.55 (1.32–4.96), P=0.006</td>
<td>2.78 (1.37–5.63), P=0.005</td>
<td>2.09 (0.99–4.42), P=0.053</td>
<td>2.23 (0.99–4.98), P=0.052</td>
</tr>
<tr>
<td>Plaque</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>1.03 (0.41–2.59), P=0.948</td>
<td>0.93 (0.35–2.46), P=0.883</td>
<td>0.89 (0.32–2.53), P=0.833</td>
<td>0.76 (0.25–2.38), P=0.641</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1.98 (1.06–3.70), P=0.032</td>
<td>1.61 (0.84–3.11), P=0.154</td>
<td>2.02 (1.05–3.89), P=0.036</td>
<td>1.57 (0.78–3.17), P=0.205</td>
</tr>
<tr>
<td>MCI excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean IMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.09 (0.90–1.33), P=0.378</td>
<td>1.10 (0.90–1.36), P=0.357</td>
<td>1.00 (0.81–1.25), P=0.988</td>
<td>1.00 (0.79–1.27), P=0.982</td>
</tr>
<tr>
<td>Dichotomous†</td>
<td>2.76 (1.43–5.32), P=0.003</td>
<td>2.98 (1.48–5.99), P=0.002</td>
<td>2.21 (1.06–4.64), P=0.036</td>
<td>2.35 (1.06–5.22), P=0.036</td>
</tr>
<tr>
<td>Plaque</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>1.20 (0.47–3.07), P=0.700</td>
<td>1.05 (0.39–2.84), P=0.918</td>
<td>0.95 (0.33–2.71), P=0.919</td>
<td>0.78 (0.25–2.46), P=0.672</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1.91 (1.02–3.61), P=0.045</td>
<td>1.55 (0.80–3.03), P=0.196</td>
<td>2.01 (1.02–3.96), P=0.043</td>
<td>1.58 (0.77–3.26), P=0.215</td>
</tr>
</tbody>
</table>

CI, confidence interval; IMT indicates intimal medial thickness; MCI, mild cognitive impairment.

*Adjusted for age, sex, race, education, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, cardiovascular disease, diabetes mellitus, and smoking.

†< 80th percentile vs ≥80th percentile (0.80 mm).

For tabular results of supplementary analyses with ApoE included as a covariate, please see Supplementary Tables I and II. Although sample sizes were reduced by 16% to 18%, results did not meaningfully change. The only differences arose for analysis of dichotomous IMT in relation to dementia and AD after exclusion of stroke, in which both HRs transitioned from nonsignificance (all P=0.05) to significance (all P=0.03).

Discussion

During up to 14 years of follow-up, we identified strong associations between multiple measures of carotid atherosclerosis and prospective risk of dementia among participants in the BLSA. Raw rates of dementia and AD among individuals in the upper quintile of carotid IMT or with bilateral plaque were generally double the rates of individuals in the lower quintiles of IMT or with no plaque, respectively. Results of Cox proportional hazards models, adjusted for demographic, biomedical, and behavioral risk factors, demonstrated similar patterns. Individuals in the upper quintile of carotid IMT had >2.5-fold increased risk of both dementia and AD during follow-up, regardless of how MCI cases were treated. Results for carotid IMT were relatively unchanged after exclusion of stroke, although select findings became marginally significant. Bilateral carotid plaque was consistently associated with >2.0-fold increased risk of dementia. We found no association between plaque and risk of AD. Log-rank tests for Kaplan-Meier survival curves showed no significant differences in median probability of dementia, although these curves do not take into account critical covariates, including age.

Taken together with existing literature, the current results suggest a threshold effect for carotid IMT and risk of dementia.
and AD. Specifically, continuous IMT was not associated with risk of dementia, whereas IMT was significant when defined as a dichotomy (ie, at the 80th percentile). Two previous studies in which carotid IMT was coded as quartiles or quintiles have shown similar threshold effects. In the Rotterdam study, only the highest quintile of carotid IMT was associated with dementia and AD risk. Further, Cardiovascular Health Study data showed only the highest quartile of carotid IMT to be associated with dementia risk. This pattern of findings is consistent with the idea that IMT must reach a criterion thickness to become statistically predictive of dementia. Although IMT has been validated as an index of systemic atherosclerosis, it is also known that increased IMT may represent nonatherosclerotic age-associated changes in the vessel wall, or an adaptive response to changes in flow, wall tension, or lumen diameter. However, IMT in the upper quintile of the distribution is less likely to reflect these normative, nonatherosclerotic processes, and thereby is more likely to be reflective of systemic atherosclerosis burden and associated dementia risk.

To our knowledge, only 1 previous study has examined carotid plaque and prospective dementia risk. In that study, there was no significant association between number of plaques and dementia risk during a median 9-year follow-up, although the relation became significant over the course of much shorter follow-up. In the present study, only bilateral plaque was associated with prospective dementia risk, potentially suggesting that bilaterality (ie, presenting greater severity/systemic presence) may be an important indicator of risk. Patterns of dementia incidence by plaque category (Table 2) also are consistent with this possibility. Although we found no association between plaque and AD-specific risk, poor observed power in this subgroup jeopardizes the validity of this finding, particularly given the magnitude of obtained HRs.

MCI has been inconsistently considered in the literature. It typically is not mentioned (and presumably included in the at-risk group) or excluded, but these 2 approaches have never been examined simultaneously. Doing so in the present study demonstrated that remarkably similar patterns arose, regardless of how MCI was treated. Inclusion of MCI in the at-risk group could unnecessarily bias results, such that imminent dementia cases are categorized as cognitively normal. However, complete exclusion of MCI reduces generalizability of results to community-based populations (where imminent dementia is unavoidable) and reduces sample sizes and associated power available for analyses. Findings from the present study suggest that inclusion of MCI cases in the at-risk group is a reasonable approach.

Several mechanisms may explain the association between atherosclerosis and dementia. A common genetic vulnerability, such as ApoE genotype, may contribute to development of both atherosclerosis and dementia. For example, AD patients carrying the ApoE ε4 allele have greater IMTs than AD noncarriers or vascular dementia patients. However, there is little evidence that an interaction exists between ApoE genotype and subclinical atherosclerosis in the prediction of future onset of dementia. Other shared cardiovascular risk factors, such as high blood pressure, also may play a role. Nonetheless, findings from the present study, as well as those from the Cardiovascular Health Study and Rotterdam studies, all withstood adjustment for a multitude of these risk factors. Subclinical cerebrovascular (eg, silent brain infarctions, white matter disease) and cerebral hyperperfusion also may link atherosclerosis and dementia. Last, neuropathologic evidence has indicated an association between atherosclerosis and severity of neocortical plaques in AD, but there is currently no consensus regarding causality.

Strengths of this investigation included its prospective design, length of follow-up, assessment of both carotid IMT and plaque, consideration of both all-cause dementia and AD, and attention to MCI and stroke in the analytic design. The study was limited by its sample size and compromised power in certain subgroup analyses. Also, frequency of vascular dementia was not high enough for separate examination, and ApoE data were not complete. In addition, the study was based on a convenience sample of typically highly educated participants. The homogeneity and nonrepresentative nature of the sample may limit the generalizability of the study, although the homogeneity of the sample also may restrict the influences of confounding demographic variables. Last, it is well-known that clinical diagnosis of AD is challenging, with true diagnosis of AD occurring only postmortem. Every precaution was taken to reduce the likelihood of misclassification, but no approach is infallible.

**Conclusion**

Overall, findings from the present study suggest that multiple measures of carotid atherosclerosis are associated with prospective risk of dementia. Individuals in the upper quintile of carotid IMT or bilateral carotid plaque were at greatest risk. These findings underscore the possibility that early intervention to reduce atherosclerosis may help delay or prevent onset of dementia and AD.

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**Disclosures**

None.

**References**


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