Embolic Signals And Prediction of Ipsilateral Stroke or Transient Ischemic Attack in Asymptomatic Carotid Stenosis

A Multicenter Prospective Cohort Study

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Background and Purpose—We tested the hypothesis that transcranial Doppler embolic signal (ES) detection identifies an increased risk of ipsilateral carotid stroke or transient ischemic attack (TIA) in subjects with asymptomatic severe carotid stenosis.

Methods—Subjects with duplex-determined 60% to 99% carotid stenosis, without other apparent cerebroembolic sources, underwent 6-monthly neurological assessment and 60-minute ES monitoring. ES positivity was defined as ≥1 ES detected in ≥1 study, ES negativity as no ES in any study, and consistent ES negativity as no ES in any study where ≥6 studies were performed. Rates of ipsilateral carotid stroke/TIA were calculated using Kaplan–Meier analysis and correlated with ES status using odds ratios (ORs) and Cox proportional hazards regression analysis.

Results—A total of 202 subjects (138 male; mean age 74 years; mean follow-up 34 months) were recruited. The average annual rate of ipsilateral carotid stroke/TIA was 3.1%. A total of 231 arteries were monitored at least once (mean 4.3 studies/artery). Six of 60 (10.0%) ES-positive arteries had an ipsilateral carotid stroke/TIA compared with 12 of 171 (7.0%) ES-negative arteries (OR, 1.47; 95% CI, 0.43, 4.48; P=0.624) and 2 of 41 (4.9%) consistently ES-negative arteries (OR, 2.17; 95% CI, 0.36, 22.90; P=0.59). Differences in survival free of ipsilateral carotid stroke/TIA according to ES status were not statistically significant.

Conclusions—Although there were more ipsilateral carotid cerebrovascular events among ES-positive arteries, this was not statistically significant. Less labor-intensive techniques are required to make further study and clinical application practical. (Stroke. 2005;36:1128-1133.)

Key Words: carotid stenosis ■ embolic signal ■ risk ■ stroke ■ transcranial Doppler

Estimates of average annual risk of ipsilateral stroke associated with asymptomatic severe (>50%) carotid stenosis approximate 2.0 to 3.3%,1–7 similar to the 2.0% to 5.0% estimated perioperative risk of stroke/death associated with carotid endarterectomy (CEA).3,4,7 Assuming results achieved in large randomized trials4,7 are widely applicable, the number of asymptomatic subjects requiring CEA to prevent 1 ipsilateral disabling stroke annually approximates 170.8 Therefore, a high-risk subgroup needs to be identified to make CEA cost–benefit-effective in this setting.

Preliminary studies suggested that transcranial Doppler (TCD) detected embolic signals (ES) and may be useful in identifying asymptomatic subjects with severe carotid stenosis at high risk of ipsilateral stroke or transient ischemic attack (TIA).9,10 However, there have been no large prospective studies confirming these findings. In addition, it remains unknown what proportion of subjects shed TCD-detected microemboli and what constitutes sufficient monitoring to identify them. The Asymptomatic Stenosis Embolus Detection (ASED) Study was an Australian multicenter, prospective, observational cohort study of asymptomatic subjects with severe (60% to 99%) carotid stenosis and without other apparent cerebroembolic sources. The hypothesis was that TCD-detected ES in subjects with asymptomatic high-grade carotid stenosis predicts an increased risk of ipsilateral carotid territory stroke or TIA.

Subjects and Methods

Subjects were recruited from the departments of Neurology at Austin Health, Box Hill Hospital and John Hunter Hospital and Vascular...
Surgery at Austin Health. The majority of subjects were identified from referrals for carotid duplex (CD), usually requested because of carotid bruit, extracerebral vascular disease, or cerebrovascular symptoms.

Inclusion criteria: (1) duplex-determined unilateral/bilateral 60% to 99% asymptomatic carotid stenosis using accepted criteria, including peak systolic velocity (PSV) of ≥150 cm/s in the proximal internal carotid artery or adjacent common carotid artery; and (2) absence of previous symptoms or signs of ischemia in the study artery territory. A history of stroke/TIA in other vascular territories or clinically “silent” radiological evidence of such events in any vascular territory was allowed.

Exclusion criteria: (1) disorders commonly associated with cerebroembolism (including prosthetic heart valves, chronic congestive cardiac failure, electrocardiographic chronic/frequent atrial fibrillation [AF], or mobile aortic arch atheroma). Echocardiography was not performed routinely; however, previous results were considered; (2) carotid stenosis after neck radiotherapy, trauma, dissection, or not performed routinely; however, previous results were considered; (3) inadequate temporal bone TCD insonation window; (4) TCD-detected ipsilateral severe carotid or middle cerebral artery stenosis; (5) lack of informed consent or ability to comply with follow-up; and (5) poor life expectancy.

Regarding censoring criteria, follow-up was discontinued from the date of CEA for a still-asymptomatic study artery or development of focal cerebrovascular symptoms. A history of stroke/TIA in other vascular territories was categorized as ischemic heart disease indicated a history of angina pectoris, myocardial infarction (fatal/nonfatal), and any death. A panel of 2 neurologists, blinded to ES detection results, validated all outcomes and censoring events.

**Definitions**

**Ischemic Events**

Stroke and transient ischemic events were differentiated using a 24-hour threshold. The diagnosis of myocardial infarction required ECG or cardiac enzyme evidence or opinion of a cardiologist/general physician.

**Vascular Risk Factors**

Hypertension, diabetes, and hypercholesterolemia were diagnosed using history or direct measurements (blood pressure of ≥160/90, fasting blood glucose of ≥7.5 mmol/L, and fasting serum cholesterol of ≥5.5 mmol/L, respectively). Current smoking was defined as any tobacco smoking in the preceding 3 months after habitual intake for ≥12 months. A past smoker had abstained for at least the previous 3 months. Ischemic heart disease indicated a history of angina pectoris, myocardial infarction, or ischemic cardiac failure. Peripheral vascular disease indicated a history of lower limb arterial insufficiency, aortic aneurysm, or atherosclerotic renal artery stenosis.

**Follow-Up**

Subjects were assessed at entry and 6-monthly with respect to cerebrovascular symptoms and signs, vascular risk factors, and use of antithrombotic medication (warfarin, aspirin, ticlopidine, clopidogrel, or dipryidamole). CD was performed at entry and 6–12 monthly thereafter. If a subject was no longer able to attend the study center, he/she was visited at home or contacted by phone. A study neurologist referred subjects with outcome and censoring events for appropriate treatment. If risk factors were poorly controlled or if lipid status was unknown, the subject’s medical practitioner(s) was encouraged to intervene.

**Neurosonology**

CD studies were performed using the ATL HDI Ultramark 9, ATL HDI 3000, ATL HDI 5000, or GE ultrasound series 700. Stenosis was categorized as <40%, 40% to 49%, 50% to 60%, 61% to 70%, 71% to 80%, 81% to 90%, 91% to 99%, or occluded. Most (90.0%) CD studies were performed at the Austin Health Neurology Department, where a recent unpublished audit of 81 cases yielded a sensitivity of 88% and a specificity of 96% of duplex techniques in detecting angiographic stenosis of ≥70%.

ES monitoring was performed for 60 minutes 6-monthly using the TC2-64 (Eden Medical Electronics) for the first 57 studies and Multidop T or Multidop T2 (DWL Elektronische System GmbH) thereafter. Insonation, using the temporal acoustic window, was performed at a depth of 50 to 60 mm using a 2-MHz pulsed Doppler transducer. The sample volume (generally 8 to 15 mm) emitted power (<100 mW), and gain were minimized to achieve an optimal ES-to-background signal relationship. A 2-channel Sony DAT machine was used to record all monitoring studies, except for bilateral cases, when an 8-channel Sony PCM-800 DAT machine was used preferentially.

Off-line ES analysis was performed in 2 stages by trained blinded observers using the EME-Nicolet Pioneer TC 2020. Initially, an observer reviewed the whole study noting the timing of possible ES. Then together, 2 observers inspected each possible ES using Consensus Committee criteria to separate typical ES (with intensity of ≥6 dB above background signal, as determined manually using the replay device color-intensity scale) from other high-intensity transient signals (HITS), including artifacts. To help standardization, all ES analysis was performed at the coordinating center (Austin Health), and 1 investigator (A.A.) helped validate every study.

An ES-positive artery was defined a priori as having ≥1 ES detected in ≥1 study. An ES-negative artery was defined a priori as having no ES during any study (≥1, depending on number performed). A consistently ES-negative artery was defined post hoc as one for which no ES were ever detected and for which ≥6 studies were performed (see below).

**Statistical Analysis**

Kaplan–Meier analysis was performed to calculate rates of outcome measures and ipsilateral carotid stroke/TIA according to ES status. Odds ratios (ORs) were calculated using an exact method with a 2-sided P value and 95% CIs (StatXact v.5; Cytel Software Corporation). Cox proportional hazards regression analysis (SYSTAT v.10; SPSS) was used to compare survival free from first ipsilateral carotid stroke/TIA with respect to ES status over the whole follow-up period.

The proportion of ES-positive arteries increased with the number of studies performed, consistent with data published by other investigators. In a supplementary analysis, to determine the minimum number of studies necessary to distinguish ES-positive and consistently ES-negative arteries, the cumulative proportion of ES-positive arteries was plotted according to number of studies performed, and 4-parameter logistic regression was applied.

**Ethical Considerations**

Ethics committee approval was obtained at each study center.

**Results**

From May 1996 to December 2000, 601 subjects were screened for study eligibility, of whom 202 subjects with 240 asymptomatic carotid arteries were recruited. A total of 138 of 202 (68%) subjects were male, and the mean age at study entry was 74 years (range 49 to 91 years). The most common reasons for exclusion were previous symptoms (16.0%), previous CEA, angioplasty, or stenting (11.8%), <60% stenosis (10.5%), inadequate TCD acoustic window (10.5%), AF (6.9%), and refusal or inability to participate (12.9%) by the time of assessment for eligibility.

Subject demographics, risk factors, and therapy are summarized in Table 1. At entry, 34 of 240 (14%) arteries were graded as 50% to 60% stenosis, 90 (38%) as 61% to 70%
TABLE 1. Characteristics of the ASED Study Cohort

<table>
<thead>
<tr>
<th>Risk Factor/Therapy</th>
<th>At Entry No. (% of cohort)</th>
<th>By Study End* No. (% of cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>138 (68)</td>
<td>155 (77)</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Contralateral ICA/Verteobasilar stroke/TIA/retinal event</td>
<td>85 (42)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Contralateral ICA occluded</td>
<td>10 (5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>146 (72)</td>
<td>127 (63)</td>
</tr>
<tr>
<td>Current smoker†</td>
<td>28 (14)</td>
<td>32 (16)</td>
</tr>
<tr>
<td>Ex-smoker†</td>
<td>120 (59)</td>
<td>127 (63)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (17)</td>
<td>37 (18)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>135 (67)</td>
<td>155 (77)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>105 (52)</td>
<td>111 (55)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>67 (33)</td>
<td>76 (38)</td>
</tr>
<tr>
<td>On antiplatelet therapy</td>
<td>178 (88)</td>
<td>187 (93)</td>
</tr>
<tr>
<td>On warfarin</td>
<td>11 (5)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>On antihypertensive therapy†</td>
<td>...</td>
<td>156 (77)</td>
</tr>
<tr>
<td>On cholesterol-lowering therapy‡</td>
<td>...</td>
<td>151 (75)</td>
</tr>
</tbody>
</table>

*Characteristic noted at entry and/or some stage during follow-up.
†Four ex-smokers at entry later restarted, and 7 smokers at entry later quit.
‡This data collection commenced soon after recruitment of the first patients.
ICA indicates internal carotid artery.

TABLE 2. ASED Study Kaplan–Meier Outcome Event Rates

<table>
<thead>
<tr>
<th>Time</th>
<th>Ipsilateral Carotid Stroke/TIA/Retinal Event</th>
<th>Ipsilateral Carotid Stroke Hemispheric</th>
<th>Any Cerebral Stroke</th>
<th>Nonstroke Death</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>4.1 (1.4, 6.8)</td>
<td>1.0 (−0.4, 2.4)</td>
<td>2.1 (0.1, 4.1)</td>
<td>3.6 (1.0, 6.2)</td>
<td>...</td>
</tr>
<tr>
<td>3 years</td>
<td>9.2 (5.2, 13.2)</td>
<td>3.1 (0.7, 5.5)</td>
<td>6.6 (3.2, 10.0)</td>
<td>18.4 (13.1, 23.7)</td>
<td>4.9 (1.9, 7.9)</td>
</tr>
<tr>
<td>5 years</td>
<td>11.7 (7.3, 16.1)</td>
<td>4.4 (1.6, 7.2)</td>
<td>9.9 (5.8, 14.0)</td>
<td>23.5 (17.7, 29.3)</td>
<td>10.6 (6.4, 14.8)</td>
</tr>
<tr>
<td>First 3-year annual average</td>
<td>3.1 (0.7, 5.5)</td>
<td>1.0 (−0.4, 2.4)</td>
<td>2.2 (0.2, 4.2)</td>
<td>6.1 (2.8, 9.4)</td>
<td>1.6 (−0.1, 3.3)</td>
</tr>
</tbody>
</table>

*Rate 95% CIs in brackets.

TABLE 3. Accumulation of ES-Positive Arteries According to No. of ES Studies

<table>
<thead>
<tr>
<th>No. of Studies Performed</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. arteries studied</td>
<td>231</td>
<td>206</td>
<td>176</td>
<td>137</td>
<td>89</td>
<td>72</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>No. ES+ arteries</td>
<td>27</td>
<td>34</td>
<td>35</td>
<td>33</td>
<td>30</td>
<td>28</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Cumulative % ES+ arteries</td>
<td>12</td>
<td>17</td>
<td>20</td>
<td>24</td>
<td>34</td>
<td>39</td>
<td>38</td>
<td>42</td>
</tr>
</tbody>
</table>

stenoosis, 38 (16%) as 71% to 80% stenosis, 30 (13%) as 81% to 90% stenosis, and 47 (20%) as 91% to 99% stenosis. One of 240 (<0.5%) study arteries (PSV 180 cm/s) was graded 40% to 49% stenosis at entry and 50% to 60% at the next examination. Two arteries (50% to 60% stenosis) had a PSV of <150 cm/s at entry, and in both cases, the PSV exceeded 150 cm/s at next examination.

There were 20 ipsilateral cerebrovascular events among 19 subjects (7 ischemic strokes, 8 hemispheric TIAs, and 5 retinal events). Outcome event rates are summarized in Table 2. The first 3-year average annual rate of ipsilateral carotid stroke/TIA was 3.1% (95% CI, 0.7, 5.5%) and ipsilateral carotid hemispheric stroke, 1.0% (95% CI, −0.4, 2.4%). Twenty arteries (from 19 subjects) were censored (CEA in 10 cases, AF in 8, prosthetic heart valve implantation in 1, and poor temporal insonation window in 1). There were no significant differences in risk factors and therapies between the 10 subjects censored because of CEA and those remaining. However, the median category of maximal carotid stenosis during follow-up was >90% among these 10 censored arteries and 71% to 80% among the remaining.

Nine of 240 (3.8%) eligible arteries, all in subjects with bilateral eligible arteries, were not monitored because of poor temporal acoustic window, limited subject availability, or symptoms occurring after recruitment and before monitoring. In total, 1017 ES detection studies were performed, including 53 (5%) that were <60 minutes (20 to 36 minutes). Seventeen of 1017 (1.7%) ES detection studies were technically inadequate, including 7 because of an artifact with recurring audible HITS abolished (with spectral preservation) by slight probe movement and that we attributed to superficial temporal artery pulsation.

There remained 1000 6-monthly studies for analysis (mean 4.3; range 1 to 10 studies per artery). A total of 231 arteries were monitored at least once, and 41 arteries were monitored a maximum of 8 to 10×. A total of 12% of arteries were ES positive after the first study and ≈42% by 8 to 10 studies (Table 3). A total of 160 ES were detected during the 1000 ES studies, producing an overall average rate of 0.16 ES per hour of monitoring. A total of 77 of 1000 (7.7%) monitoring studies were ES positive, and in 48 of these, only 1 ES was detected (median 1; range 1 to 11).

Overall, ES were detected at least once in 60 of 231 (26%) monitored arteries (mean 5.3 studies per ES-positive artery), and the average hourly rate of ES detection among them was 0.51. A total of 47 of 60 (78%) of ES-positive arteries were ES positive during just 1 study, 11 of 60 (18%) during 2, and 2 of 60 (3%) during 4 studies. Only 1 artery was ES positive on every occasion (4 6-monthly and 8 additional studies). In 171 of 231 (74%) monitored arteries, no ES were detected (mean 4.1 studies per ES-negative artery). There were 41 consistently ES-negative arteries (ES negative in ≥6 studies).

There were 18 ipsilateral carotid cerebrovascular events among the 231 monitored arteries (6 ischemic strokes, 8 hemispheric TIAs, 1 retinal infarction, and 3 amaurosis fugax). Six of 60 (10%) ES-positive arteries and 12 of 171 (7%) ES-negative arteries monitored at least once became symptomatic (OR, 1.47; 95% CI, 0.4, 4.48; exact 2-sided P = 0.62). Kaplan–Meier (Figure 1) 5-year ipsilateral carotid stroke/TIA rates were 17.0% for ES-positive and 8.6% for ES-negative arteries. Cox proportional hazards regression analysis showed no significant difference between the 2
groups over the entire 5.9-year follow-up period (2-sided $P$ value=0.859). Among all 231 monitored arteries, the sensitivity of detecting any ES in predicting ipsilateral carotid stroke/TIA was 33.3% (95% CI, 26.9, 39.1%), specificity was 74.6% (95% CI, 69.4, 80.6%), positive predictive value was 10.0% (95% CI, 6.1, 13.9%), and negative predictive value was 93.0% (95% CI, 89.7, 96.3%).

As mentioned, an artery was more likely to become ES positive with the number of studies performed. Four-parameter logistic regression analysis of the relationship between ES positivity and number of TCD ES studies performed (Figure 2) revealed a sigmoidal distribution ($r^2=0.976$), with a leveling off in detection of new ES-positive arteries after $\approx 6$ studies. The upper limit of this curve indicated that a maximum of $\approx 41\%$ of arteries would be identified as ES positive using this monitoring protocol (95% CI, 36.7, 45.1), and that $\approx 6$ studies would be required to identify them.

To make sure an association between ES detection and risk of ipsilateral stroke/TIA was not missed because of inclusion of infrequently monitored ES-negative arteries, we compared the outcome of the 60 ES-positive arteries with that of the 41 consistently ES-negative arteries monitored at least 6× (2, or 4.9%, of which became symptomatic; OR, 2.17; 95% CI, 0.36, 22.90; exact 2-sided $P=0.588$). Kaplan–Meier (Figure 3) 5-year ipsilateral carotid stroke/TIA rates were 17.0% for ES-positive arteries and 2.5% for consistently ES-negative arteries. Cox proportional hazards regression analysis showed no significant difference in survival between these 2 groups (2-sided $P=0.20$). Among these 101 “best” monitored arteries, the sensitivity of detecting any ES in predicting ipsilateral carotid stroke/TIA was 75.0% (95% CI, 66.6, 83.5%), specificity was 41.9% (95% CI, 32.4, 51.6%), positive predictive value was 10.0% (95% CI, 4.2, 15.9%), and negative predictive value was 95.1% (95% CI, 90.8, 99.3%).

**Discussion**

In this study of subjects with asymptomatic severe carotid stenosis, those who had ES-positive arteries had more ipsilateral carotid ischemic events. However, this finding was not statistically significant, even allowing for infrequently monitored ES-negative arteries. Therefore, our results do not prove the hypothesis that ES detection selects high-risk subjects with asymptomatic severe carotid stenosis who could benefit from CEA, as proposed on the basis of several small pilot studies and supported by preliminary data from another prospective cohort study. Publication of results from a third ongoing prospective cohort study or a meta-analysis may be necessary to resolve this question.

In the ASED study, more conclusive analysis was limited by the low rates of cerebrovascular events and ES detection in this population. The ASED study average annual rates of ipsilateral carotid stroke/TIA and stroke alone were only 3.1% and 1.0%, respectively. It is unlikely that stroke events were missed because subjects were assessed at 6-monthly intervals, every effort was made to ensure effective communication with other medical practitioners, and no subjects were lost to follow-up. It is also unlikely that the small number of asymptomatic arteries censored because of CEA...
had any significant impact on the results. These 10 subjects were selected for surgery at the discretion of their nonstudy medical practitioners according to perceived risk. However, no factors that identify higher-than-average risk in this population (including degree of stenosis, progressive stenosis, or ultrasonic plaque characteristics) have yet been identified. These 10 censored arteries had a higher median-maximal degree of stenosis (>90%) during follow-up, and yet, there is evidence that near-occlusion is protective.

No larger prospective observational cohort studies of subjects with asymptomatic severe carotid stenosis have yet been published, and most estimates of the associated risk of ipsilateral stroke or TIA are based on small samples, limiting comparisons. However, our rates are lower than reported previously and add to a progressive fall in ES detection rates from other studies published over the last 20 years (Table I, available online only at http://www.strokeaha.org). Methodological differences, such as the exclusion and censoring of subjects with other cerebroembolic sources, may have contributed to our low cerebrovascular event rates. However, if the fall in risk estimates since the early 1980s corresponds to a real fall in risk, this would be consistent with the recently reported 40% fall in stroke incidence in the United Kingdom attributed to improved vascular risk factor management or a declining risk factor prevalence.

A major finding of the ASED study was that generally, ES detection rates in relation to severe asymptomatic carotid stenosis are very low, in keeping with earlier work. In the ASED study, there were average hourly ES detection rates of 0.16 and 0.51, respectively, in the overall cohort and among controls. These rates are lower than those associated with symptomatic carotid stenosis and higher than in asymptomatic controls.

The ASED study results show that many hours of monitoring are required to identify the ES-negative artery and imply the importance of adequately monitoring arteries before assigning ES status. When the results of 130 “ES-negative” arteries monitored <6× were removed from the analysis, the sensitivity of the technique rose from 33% to 75%. The low positive predictive value of detecting any ES in this study suggests that most subjects tolerate the microembolic load well because the plaque inflammation settles sufficiently or the cerebral circulation copes. The high negative predictive value suggests that ES-negative arteries are likely to remain asymptomatic during the observation period. One would expect from our results that at most, ~41% of asymptomatic highly stenotic carotid arteries would be ES positive on the basis of biannual 60-minute monitoring studies. The proportion of embolizing arteries may have been higher if more frequent or prolonged monitoring was used.

It has been estimated, on the basis of the ASED study, that the required sample size to test the hypothesis that the detection of any ES can be used to identify subjects with asymptomatic severe carotid stenosis at high risk of ipsilateral carotid stroke/TIA is ~500 to 2000 subjects, depending closely on outcome event rates. A still larger study would be required to show the significance of different rates of microembolism in these subjects. Currently, there are no published data to allow comparison of the yield from a single prolonged ES study with repeated short studies.

The manual method of ES detection used in the ASED study was the most reliable at the time. However, it proved extremely labor-intensive and would be impractical in clinical practice for subjects with asymptomatic carotid stenosis. However, many limitations may be overcome using new techniques for automated ES analysis, ambulatory monitoring, and by “Power M-Mode Doppler.” The last technique, in which many sampling gates are used so an embolus can be tracked as it moves through the vessel, provides a new and more specific criterion for ES detection.

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References


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