Correlation Between Carotid Intraplaque Hemorrhage and Clinical Symptoms

Systematic Review of Observational Studies

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Background and Purpose—We sought to investigate the association between carotid intraplaque hemorrhage (IPH) and ipsilateral symptoms of cerebral ischemia.

Methods—A search was performed for clinical observational studies comparing the incidence of IPH between symptomatic and asymptomatic patients. Odds ratios (ORs) for IPH as a factor in the pathogenesis of neurologic events were calculated and combined by a meta-analysis. Interstudy heterogeneity, estimated effects, and methodologic quality of the studies were assessed.

Results—Thirty-one studies were included for analysis. The reported ORs varied widely. Overall, the incidence of IPH in the symptomatic groups was significantly higher than in the asymptomatic group. However, there was an apparent trend for heterogeneity ($P<0.00001$) between studies. The random-effects summary estimator of ORs was 2.25 (95% CI, 1.57 to 3.22; $P<0.00001$). To identify potential sources of heterogeneity, subgroup analyses were performed. The pooled ORs varied greatly by stratification. Major heterogeneity was found among studies with low quality, microscopic methods of examination, significant effects, small sizes, early publication, and unequal severity of carotid stenosis in both groups. Large, recent, macroscopic, or high-quality studies, as well as studies with equal degrees of stenosis, tended to yield insignificant associations. The methods in defining and evaluating hemorrhage were very heterogeneous. Characterizations of the age, size, number, and location of hemorrhages were poorly reported and highly variable. In addition, a lack of control of confounders and selection bias were frequently identified among studies.

Conclusions—Statistical inferences have suggested a plausible role in the production of cerebral ischemia; however, reliable interpretation was strongly undermined by poor methodologic quality, substantial heterogeneity, and suspicious publication bias. To precisely estimate the underlying correlation, a well-designed study with uniformity in definition and evaluation for IPH might be warranted. (Stroke. 2007;38:2382-2390.)

Key Words: asymptomatic carotid stenosis • endarterectomy • intraplaque hemorrhage • symptomatic carotid stenosis

Intraplaque hemorrhage (IPH) is a common feature of carotid atherosclerotic plaques. There has been considerable emphasis on the role of IPH in the pathogenesis of cerebral ischemic symptoms after extensive clinicopathologic analysis. Unfortunately, conflicting evidence has been presented for and against the role of IPH as an indicator of subsequent symptoms.

The concept of IPH was originally brought into perspective by Imparato et al1 in 1979, who stressed that IPH was frequently associated with focal neurologic symptoms and played a significant role in the progression of carotid plaques. Later, a follow-up series showed that IPH was the only grossly morphological characteristic that contributed to the production of symptoms.2 However, it was reported that a correlation could not be corroborated, and the mere presence of IPH at the carotid bifurcation did not necessarily produce symptoms.3–5 Most recently, Milei et al6 found that IPH was not potentially associated with symptoms, and it appeared that IPH might occur at any time, irrespective of symptoms. Moreover, the age of IPH (acute, recent, or old) and its role have been the subject of disagreement.1,3–16 Quite a few studies have indicated that the presence of IPH appears to increase with the severity of carotid artery stenosis.2,4,5,13,16–23 Some attention has focused on the quantification of hemorrhage volume.5,24–26 Although a summation analysis27 was performed among 7 studies5,9–11,17,28,29 with equal severity of stenosis, a comprehensive review was still unavailable.

This study was undertaken to present a systematic review of the literature, with the aim of summarizing and synthesizing all of the data available since the first report. Furthermore, we sought to estimate the effect sizes,
evaluate the quality of the primary studies individually, search for possible publication bias, and identify and explain potential sources of heterogeneity in results across studies.

Materials and Methods

Search Strategy
We identified (1) studies in English published between January 1979 and September 2006, inclusive, by comprehensive text words and MeSH-based electronic searches of MEDLINE (Entrez PubMed NIH) and (2) electronic search terms, which included carotid stenosis/plaque, patholog*, histolog*, microscop*, macroscop*, gross, intraplaque h*emorrhage, intramural h*emorrhage, or subintimal h*emorrhage. (3) The abstract of each article was carefully reviewed to detect appropriate publications; (4) Reference lists of all relevant articles were checked for further leads; and (5) Additionally, we performed a manual search of the Stroke and Journal of Vascular Surgery journals.

Inclusion Criteria
Studies were included if (1) specimens were harvested at endarterectomy procedures and the pathologic features of IPH were characterized; (2) they compared the incidence of IPH between symptomatic and asymptomatic patients or plaques; and (3) basic data regarding the frequency of IPH were provided for both groups.

There were 2 methods used to define IPH: microscopic (histologic) examination and macroscopic (gross) inspection. Specimens should be removed intact to avoid misleading pathologic findings. Histologic features were evaluated by examining sections for the presence of IPH. Patients or plaques were defined as symptomatic when focal symptoms of cerebral ischemia were present, ipsilateral to the carotid lesions, such as transient ischemic attack, amaurosis fugax, reversible ischemic neurologic deficit, or stroke. Asymptomatic plaques were taken from patients without symptoms or from the side without symptoms in those undergoing bilateral operations.

Exclusion Criteria
Studies that met 1 of the following items were excluded: (1) animal studies, case reports, editorials, letters, and reviews; (2) highly selected studies (symptomatic or asymptomatic population only); (3) those with very different group sizes; (4) those that failed to characterize the pathologic features regarding IPH; (5) nonatherosclerotic carotid stenosis (eg, fibromuscular dysplasia, postradiotherapy); and (6) restenosis reports (eg, occurring after endarterectomy or carotid angiography and stenting). Multiple publications from the same project were eliminated from the meta-analysis, and the 1 that was most appropriate to this review was selected.

Data Extraction
The following general descriptive information was extracted from each study: (1) type of population; year of publication; country of origin; number, age, and sex of participants; plaque number; methods and criteria used in determining the degree of carotid stenosis; (2) definitions of the presence and absence of ischemic symptoms; (3) time intervals between the latest onset of ischemic symptoms and surgery or pathologic examinations; (4) methods of evaluation for IPH: macroscopy or microscopy, blinded assessment or not; position, plane, stains, number, and frequency of histologic sections; (5) definition and classification of IPH; (6) numbers of patients or plaques with IPH assigned to each group; (7) characterization of the age, size, number, or location of IPH; (8) risk factors for atherosclerosis; and (9) results and conclusions of each study. Three of the authors (P.G, Z.-q.C, and F.L) selected the studies to be included in this review, extracted the data independently, and cross- checked them, with disagreement resolved by consensus.

Methodologic Quality Assessment
The quality of the included studies was evaluated individually. Blinded to each other’s assessment, 2 reviewers (P.G and F.L) scored the studies by the following criteria. One point each was given if a study: (1) recruited patients consecutively; (2) defined both symptomatic and asymptomatic patients or plaques clearly; (3) indicated the time interval between the procedures and the latest onset of ischemic symptoms; (4) defined or classified IPH specifically; (5) characterized the age, size, number, or location of hemorrhages; and (6) evaluated IPH in a blinded fashion. Studies were then stratified into 3 groups if they met 1 or 2, 3 or 4, and 5 or 6 quality criteria.

Statistical Analysis
We calculated the odds ratio (OR) for each study. The statistical validity of aggregating the studies was assessed with χ² for heterogeneity by means of a standard fixed-effect model of overview. (P<0.1 suggests that the assumption of homogeneity was violated.) Because we observed an apparent trend for heterogeneity, a random-effect model was used to combine the effects of the included studies. When the value of the OR was >1, the risk of IPH was greater within symptomatic groups.

To identify possible sources of heterogeneity, subgroup analyses were performed, including methods of definition (microscopy versus macroscopy), the age of IPH (studies were divided into those in which only acute or recent IPHs were considered and those in which the age of IPH was not explored or the number of acute IPHs was not noted), study sizes (small, <100; intermediate, 100 to 300; and large, >300), individual results (significant versus insignificant), year of publication (studies were divided into those published before and after 1995, mainly because the introduction of preventive treatment, statins in particular, could have attenuated the presence of ischemic symptoms since the mid-1990s), geographic location (native United States versus international studies), and whether specimens were from groups with equal severity or not (equal versus unequal or not stated).

The meta-analysis was performed with RevMan (version 4.2.8). Potential publication bias was assessed with an inverted-funnel plot for asymmetry. The methods of Egger and Smith,30 Begg and Mazumdar,31 and Macaskill et al32 were used to test publication bias objectively (version 9.0, STATA). A cutoff probability value of 0.1 was used as the positive threshold bias to assess the power of the statistical test.

Results
Seventy potentially relevant studies were identified. We excluded 17 that were validation studies comparing plaque imaging with histology33–49,7 that failed to provide sufficient data for each group58,59; 4 that were highly selected studies60–62; 2 that included patients with extracranial restenosis58,59; and 8 that were duplicate records.1,3,5,14,21,60–62 The group sizes were very different in 1 study.16

Of the remaining 31 eligible articles, 15 were conducted in the United States. Twenty-one studies recruited patients consecutively,* and 10 did not indicate the specifications. Eight studies harvested plaques from groups with equal severity of stenosis.‡ Both the presence and absence of ischemic symptoms were defined clearly in 13 studies.‡ The presenting symptoms were further subtyped into transient symptoms (transient ischemic attack or amaurosis fugax) and prior stroke among 4 studies.1,12,22,23,64

Thirty-one studies included 4195 patients with 4447 carotid plaques. An average age of 67.3 years old was found among 20 studies. A male-to-female ratio (2:1) was found among 17 studies. The number of carotid plaques in the studies ranged from 19 to 1008 (median, 89). There were
TABLE 1. Characteristics of Included Studies (Ordered by Year of Publication)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Methods of Evaluation</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Age, No., Size, or Location of IPH*</th>
<th>Severity of Stenosis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lusby7</td>
<td>1982</td>
<td>USA</td>
<td>+</td>
<td>79</td>
<td>49/53</td>
<td>7/26</td>
<td>70.9</td>
</tr>
<tr>
<td>Imparato2</td>
<td>1983</td>
<td>USA</td>
<td>+</td>
<td>376</td>
<td>94/275</td>
<td>21/101</td>
<td>30.6</td>
</tr>
<tr>
<td>O’Donnell*</td>
<td>1985</td>
<td>USA</td>
<td>+</td>
<td>52</td>
<td>16/26</td>
<td>10/26</td>
<td>35.0</td>
</tr>
<tr>
<td>Ammar15</td>
<td>1986</td>
<td>USA</td>
<td>+ ...</td>
<td>76</td>
<td>42/44</td>
<td>25/32</td>
<td>88.2</td>
</tr>
<tr>
<td>Fisher71</td>
<td>1986</td>
<td>USA</td>
<td>+</td>
<td>90</td>
<td>28/57</td>
<td>63/33</td>
<td>37.8</td>
</tr>
<tr>
<td>Persson‡‡</td>
<td>1986</td>
<td>USA</td>
<td>+</td>
<td>160</td>
<td>93/98</td>
<td>38/62</td>
<td>81.9</td>
</tr>
<tr>
<td>Ricotta6‡</td>
<td>1986</td>
<td>USA</td>
<td>+ +</td>
<td>74</td>
<td>26/55</td>
<td>5/19</td>
<td>41.9</td>
</tr>
<tr>
<td>Fryer§</td>
<td>1987</td>
<td>Australia</td>
<td>+ +</td>
<td>91</td>
<td>58/71</td>
<td>9/20</td>
<td>73.6</td>
</tr>
<tr>
<td>Lenninhan4</td>
<td>1987</td>
<td>USA</td>
<td>+ ...</td>
<td>198</td>
<td>56/122</td>
<td>40/76</td>
<td>48.5</td>
</tr>
<tr>
<td>Abu Rahman*</td>
<td>1990</td>
<td>USA</td>
<td>+ +</td>
<td>154</td>
<td>61/101</td>
<td>5/53</td>
<td>42.9</td>
</tr>
<tr>
<td>Avr*‡‡‡†</td>
<td>1991</td>
<td>France</td>
<td>+ +</td>
<td>187</td>
<td>12/72</td>
<td>2/115</td>
<td>7.5</td>
</tr>
<tr>
<td>Feeley§‡</td>
<td>1991</td>
<td>Ireland</td>
<td>+ +</td>
<td>52</td>
<td>25/44</td>
<td>3/8</td>
<td>37.5</td>
</tr>
<tr>
<td>Sterpetti‡</td>
<td>1991</td>
<td>USA</td>
<td>+ +</td>
<td>111</td>
<td>30/44</td>
<td>25/67</td>
<td>49.5</td>
</tr>
<tr>
<td>Maravic‡‡</td>
<td>1991</td>
<td>Greece</td>
<td>+ +</td>
<td>38</td>
<td>14/15</td>
<td>21/23</td>
<td>91.3</td>
</tr>
<tr>
<td>Damm‡‡‡</td>
<td>1992</td>
<td>Belgium</td>
<td>+ +</td>
<td>134</td>
<td>44/93</td>
<td>29/41</td>
<td>54.5</td>
</tr>
<tr>
<td>Arapoglou‡‡</td>
<td>1994</td>
<td>Greece</td>
<td>+ ...</td>
<td>89</td>
<td>44/57</td>
<td>12/32</td>
<td>62.9</td>
</tr>
<tr>
<td>Fisher‡§</td>
<td>1994</td>
<td>USA</td>
<td>+ ...</td>
<td>94</td>
<td>17/32</td>
<td>45/62</td>
<td>66.0</td>
</tr>
<tr>
<td>Seeger*</td>
<td>1995</td>
<td>USA</td>
<td>+ +</td>
<td>43</td>
<td>10/21</td>
<td>12/22</td>
<td>51.2</td>
</tr>
<tr>
<td>Sitzer‡‡‡</td>
<td>1995</td>
<td>USA</td>
<td>+ +</td>
<td>39</td>
<td>6/27</td>
<td>2/12</td>
<td>20.5</td>
</tr>
<tr>
<td>Catt*‡‡‡</td>
<td>1996</td>
<td>USA</td>
<td>+ +</td>
<td>44</td>
<td>16/19</td>
<td>14/25</td>
<td>68.2</td>
</tr>
<tr>
<td>Bassiony††</td>
<td>1997</td>
<td>USA</td>
<td>+ +</td>
<td>99</td>
<td>11/59</td>
<td>7/40</td>
<td>18.2</td>
</tr>
<tr>
<td>Park‡‡‡</td>
<td>1998</td>
<td>USA</td>
<td>+ +</td>
<td>1008</td>
<td>191/623</td>
<td>108/385</td>
<td>29.7</td>
</tr>
<tr>
<td>Yamamoto‡‡‡</td>
<td>1998</td>
<td>Japan</td>
<td>+ +</td>
<td>63</td>
<td>38/51</td>
<td>4/12</td>
<td>66.7</td>
</tr>
<tr>
<td>McCarthy‡‡‡</td>
<td>1999</td>
<td>UK</td>
<td>+ +</td>
<td>28</td>
<td>8/13</td>
<td>3/15</td>
<td>39.3</td>
</tr>
<tr>
<td>Montauban‡‡‡</td>
<td>1999</td>
<td>Netherlands</td>
<td>+ +</td>
<td>47</td>
<td>31/33</td>
<td>10/14</td>
<td>87.2</td>
</tr>
<tr>
<td>Ballotta‡‡‡</td>
<td>2000</td>
<td>Italy</td>
<td>+ +</td>
<td>457</td>
<td>96/289</td>
<td>59/168</td>
<td>33.9</td>
</tr>
<tr>
<td>Tegos‡‡‡‡</td>
<td>2000</td>
<td>USA</td>
<td>+ +</td>
<td>71</td>
<td>31/46</td>
<td>19/25</td>
<td>70.4</td>
</tr>
<tr>
<td>Storik‡</td>
<td>2002</td>
<td>Australia</td>
<td>+</td>
<td>109</td>
<td>53/71</td>
<td>29/38</td>
<td>75.2</td>
</tr>
<tr>
<td>Mile‡‡‡‡‡‡‡</td>
<td>2003</td>
<td>Argentina</td>
<td>+ +</td>
<td>281</td>
<td>31/133</td>
<td>43/148</td>
<td>26.3</td>
</tr>
<tr>
<td>Tziakas‡‡‡</td>
<td>2005</td>
<td>Greece</td>
<td>+ +</td>
<td>19</td>
<td>5/11</td>
<td>2/8</td>
<td>36.8</td>
</tr>
<tr>
<td>Turu‡‡‡‡‡‡‡</td>
<td>2006</td>
<td>Spain</td>
<td>+ +</td>
<td>84</td>
<td>27/55</td>
<td>11/29</td>
<td>45.2</td>
</tr>
</tbody>
</table>

Macro indicates macroscopic inspection; Micro, microscopic examination.
*The age, No., size, or location of IPHs were characterized.
†Carotid plaques were collected from both groups with equal degrees of carotid stenosis.

2710 symptomatic plaques and 1737 asymptomatic plaques (ratio, 1.6:1), altogether. Associated risk factors were equally distributed in 5 studies, but were not stated in the remaining reports. The time intervals between the latest onset of symptoms and surgery were available from 16 studies, with great variation.

Plaque specimens were evaluated in 6 studies by microscopy, in 10 by microscopy, in 14 by a combination of both, and were not found in 1. For the purpose of statistical comparison, microscopy plus macroscopy were combined into the microscopic category. Definitions of IPH were specified in 23 studies, and the methods in defining and evaluating hemorrhage were very heterogeneous. Histologic sections or gross features were assessed in a blinded manner in 13 studies. Eighteen studies presented the staining techniques. At least 8 different stains were used, including the routine hematoxylin and eosin. The reported incidence of IPH was highly variable in the literature (7.5% to 92.1%; median, 50.0%). A positive association was found in 23 studies, and the methods in defining and evaluating hemorrhage were very heterogeneous.
Overall Effect
We began with a fixed-effect model for our analysis. The magnitudes of overall differences between symptomatic and asymptomatic groups were statistically significant. However, a heterogeneity test indicated an extreme trend for heterogeneity among studies (Cochran’s $Q = 147.6$, $I^2 = 79.7\%$, $P = 0.00001$). Estimated effect size was then combined by use of a random-effect model. The effects ranged from 0.37 to 33.25 (median, 2.50). Subcategory analyses that aimed to seek a thorough consideration of possible sources of heterogeneity were performed (Table 1).

Subcategory Analysis
The methodologic quality of studies could account for some of the heterogeneity and made an impact on the strength of effects. Studies that fulfilled at least 5 quality criteria showed an insignificant association of symptoms with IPH and a slightly mitigated problem of heterogeneity, compared with those that fulfilled fewer than 5 quality criteria. A negative effect was found among gross inspection studies, whereas studies based on histology showed a significantly stronger effect. There was substantial heterogeneity among histologic studies. Specifically, the effect was magnified when only acute (recent) IPH was considered, and effect was diminished when age was not explored. To detect heterogeneity in relation to study size, we stratified them into tertiles according to plaque number. Large studies showed a conservative estimate and minor heterogeneity. There was less heterogeneity among negative studies compared with positive studies. Studies were dichotomized at 1995. We observed a null correlation among studies published after 1995, whereas a significant role for IPH in the cause of symptoms was observed among earlier studies (before 1995). Similar ORs and heterogeneity were found among native United States and international studies. Studies were further categorized into those with equal and unequal severity of stenosis in both groups. The pooled OR varied greatly by study stratification, and results of subgroup analyses are summarized in Table 2.

It could be generalized by careful scrutiny of Table 2 that minor heterogeneity appeared among studies with high scoring,

### Table 2. Pooled ORs and 95% CIs in Different Studies

<table>
<thead>
<tr>
<th>Types of Studies Combined</th>
<th>n</th>
<th>OR*</th>
<th>95% CI</th>
<th>$I^2$</th>
<th>Test for Heterogeneity</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>31</td>
<td>2.25</td>
<td>1.57–3.22</td>
<td>79.7%</td>
<td>$&lt;0.00001$</td>
<td>$&lt;0.00001$</td>
</tr>
<tr>
<td>Assessment of study quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulfiling $\leq2$ quality criteria</td>
<td>6</td>
<td>4.29</td>
<td>1.42–12.93</td>
<td>83.7%</td>
<td>$&lt;0.0001$</td>
<td>0.01</td>
</tr>
<tr>
<td>Fulfiling 3 or 4 quality criteria</td>
<td>19</td>
<td>2.02</td>
<td>1.29–3.17</td>
<td>78.2%</td>
<td>$&lt;0.00001$</td>
<td>0.002</td>
</tr>
<tr>
<td>Fulfiling $\geq5$ quality criteria</td>
<td>6</td>
<td>1.54</td>
<td>0.81–2.94</td>
<td>67.3%</td>
<td>0.009</td>
<td>0.19</td>
</tr>
<tr>
<td>Methods of evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic examination</td>
<td>24</td>
<td>2.57</td>
<td>1.54–4.29</td>
<td>82.0%</td>
<td>$&lt;0.00001$</td>
<td>0.0003</td>
</tr>
<tr>
<td>Macroscopic inspection</td>
<td>6</td>
<td>1.25</td>
<td>0.93–1.70</td>
<td>35.6%</td>
<td>0.17</td>
<td>0.14</td>
</tr>
<tr>
<td>Not found</td>
<td>1</td>
<td>5.85</td>
<td>1.51–22.67</td>
<td>79.1%</td>
<td>$&lt;0.00001$</td>
<td>0.002</td>
</tr>
<tr>
<td>Age of IPH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not explored</td>
<td>26</td>
<td>2.06</td>
<td>1.41–2.99</td>
<td>79.1%</td>
<td>$&lt;0.00001$</td>
<td>0.0002</td>
</tr>
<tr>
<td>Only acute (recent) IPH</td>
<td>5</td>
<td>3.55</td>
<td>1.15–11.01</td>
<td>79.3%</td>
<td>0.0007</td>
<td>0.03</td>
</tr>
<tr>
<td>Carotid plaque No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, $&lt;100$</td>
<td>20</td>
<td>2.65</td>
<td>1.64–4.29</td>
<td>64.9%</td>
<td>$&lt;0.0001$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Intermediate, 100 to 300</td>
<td>8</td>
<td>2.28</td>
<td>0.91–5.72</td>
<td>90.3%</td>
<td>$&lt;0.00001$</td>
<td>0.08</td>
</tr>
<tr>
<td>Large, $&gt;300$</td>
<td>3</td>
<td>1.21</td>
<td>0.84–1.75</td>
<td>60.5%</td>
<td>0.08</td>
<td>0.29</td>
</tr>
<tr>
<td>Individual results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant studies</td>
<td>12</td>
<td>6.41</td>
<td>3.91–10.49</td>
<td>60.8%</td>
<td>0.003</td>
<td>$&lt;0.00001$</td>
</tr>
<tr>
<td>Insignificant studies</td>
<td>19</td>
<td>1.02</td>
<td>0.79–1.31</td>
<td>37.9%</td>
<td>0.05</td>
<td>0.88</td>
</tr>
<tr>
<td>Year of publication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1995</td>
<td>17</td>
<td>3.23</td>
<td>1.76–5.90</td>
<td>84.2%</td>
<td>$&lt;0.00001$</td>
<td>0.0001</td>
</tr>
<tr>
<td>After 1995</td>
<td>14</td>
<td>1.25</td>
<td>0.92–1.70</td>
<td>41.5%</td>
<td>0.05</td>
<td>0.16</td>
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<td>US native studies</td>
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<td>2.68</td>
<td>1.56–4.58</td>
<td>84.3%</td>
<td>$&lt;0.00001$</td>
<td>0.0003</td>
</tr>
<tr>
<td>International studies</td>
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<td>1.14–3.09</td>
<td>72.5%</td>
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<td>0.01</td>
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<td>Degree of carotid stenosis</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Unequal</td>
<td>23</td>
<td>2.50</td>
<td>1.64–3.81</td>
<td>84.2%</td>
<td>$&lt;0.00001$</td>
<td>$&lt;0.0001$</td>
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<tr>
<td>Equal</td>
<td>8</td>
<td>1.44</td>
<td>0.82–2.52</td>
<td>19.3%</td>
<td>0.28</td>
<td>0.20</td>
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</table>

*Values were calculated with a random-effect model.
†$I^2$ described the amount of heterogeneity among studies relative to the total variability among the effect estimates. A value of 0% indicated no observed heterogeneity, with 25%, 50%, and 75% used as thresholds for low, moderate, and high heterogeneity, respectively.
insignificant effects, larger sizes, macroscopic evaluation, recent publication (after 1995), and equal severity of stenosis. Stronger associations were found among studies with low quality, small size, macroscopic evaluation, early publication (before 1995), specifications of IPH age, and unequal degree of stenosis.

**Definition of IPH**
The methods used for defining IPH ranged remarkably, from visual inspection of gross sections, microscopic evidence of red blood cells, histologic evidence of hemosiderins, fibrins, and siderophages to a combination of all degenerated blood constituents. In the 2 largest gross inspection studies, old hemosiderin-laden plaques were also considered examples of IPH. For macroscopy, IPH was usually characterized by its immediate recognition or on transecting the plaques at the time of arteriotomy. Studies in which light microscopy was performed were based on a broad definition of hemorrhage. In the report of Milei et al, only extensive hemorrhage with disruption of erythrocytes and that resulting in some distortion of the structure were considered. Sitzer et al defined IPH as bleeding within the plaque of >1500 µm at its largest diameter. Another study indicated that only areas of hemorrhage occupying at least 30% of the plaque section were taken into account.

**Age of the IPH**
The criteria for determining age were very heterogeneous. Frequently, the presence of IPH of different ages was observed inside 1 single lesion. The age of IPH was initially explored by Lusby et al and Ammar et al, who suggested a critical role of acute (recent) and repeated hemorrhage in the development of neurologic accidents, respectively. However, when remote hemorrhage was also taken into consideration, the differences between the 2 groups lost significance. To estimate the age of IPH, considerable work was done, and a modified elastochrome stain that could clearly delineate hemorrhages was introduced for the first time. Three pathologic categories were defined: acute (<1 week), recent (1 to 6 weeks), and remote (>6 weeks) hemorrhage. An age of 4 weeks was used as the threshold for recent and old hemorrhage in the report of Lenninhan et al, wherein there was no association between acute hemorrhage and the onset of ipsilateral symptoms. Recent (or “significant”) hemorrhage was otherwise graded when it involved >50% of the plaque thickness. Bassiouny et al diametrically defined recent IPH as collections of erythrocytes within the plaque matrix. The subsequent 2 studies in which acute IPHs were considered showed negative associations. The study by Milei et al also found that no relation could be established between the 2 groups with respect to old, distal, and laminar hemorrhages.

Old or remote hemorrhages were usually recognized by the presence of macrophages with hemosiderins or fibrins by the presence of fibrin. When hemosiderins appeared, an age of several weeks could be assumed. Fibrins likely represent chronic hemorrhages within the plaque. Perl’s test (Prussian blue) was used to detect hemosiderins and fibrins. Siderophages in the iron-stained sections were taken as evidence of remote hemorrhages. In the study of Van Maravic et al, Ladewig’s stain and Perl’s test were combined to identify siderophages or fibrins.

A repeated hemorrhage was noted when it contained >1 stage of pathologic category. Two studies did not indicate how to date the time of hemorrhage. Without specific staining, age could not be differentiated. There was no attempt to distinguish IPH age in 2 gross inspection studies with the largest sizes.

**Size, Number, and Location of IPH**
Three studies specified the size of IPH. Lenninhan et al defined large hemorrhages as those occupying ≥50% of the cross-sectional diameter. Size was similarly defined as small (<10% plaque thickness), medium (10% to 50%), and large (>50%). Araopoulos et al found that there was no significant difference regarding the extent of hemorrhage (≥25% plaque thickness) between groups. Among all of the potentially relevant studies, the volume of IPH was quantified in 4 studies, with various methods of determination. One was included for our meta-analysis, and were excluded because of insufficient data or duplicate records. The extent of IPH was quantified in relation to the total cross-sectional plaque area in the study of Bassiouny et al. Those authors concluded that IPH was commonly seen in both groups. Hatsu kami et al estimated the volume of hemorrhage with the use of computer software, and they found that volume was similar regardless of preoperative symptoms. In the report of Montauban et al, an insignificant result was reproduced and the contribution of IPH to total plaque volume was very small. Two studies found that multiple IPHs were seen more frequently in symptomatic plaques. Multiple IPHs were defined when the plaque had both new and old hemorrhage. Single IPH was considered when only 1 type of hemorrhage was present. IPHs were also explored according to their location—deep, subintimal, and communicating with the arterial lumen. Bornstein et al found that IPHs, for the most part, were deeply located (63%) and infrequently connected to the lumen. Subintimal IPH was identified when gross hemorrhages could be seen within the plaque contents beneath the intima. A break in the endothelium over the hemorrhage was noted by Persson et al, who found that IPH led to transient ischemic attack when a connection developed between the IPH and the lumen. Montauban et al also found that the location of the IPH seemed random from proximal to distal. Additionally, IPH was classified according to its degree. Laminar hemorrhages were defined as thin areas located between the layers of the media.

**Publication Bias**
Funnel plotting showed a suspicious presence of asymmetry (the Figure). Formal testing indicated conflicting evidence for publication bias (P = 0.503, 0.135, and 0.003 for the tests of Macaskill et al, Begg and Mazumdar, and Egger and Smith, respectively).

**Discussion**
Although the overall effect suggested a moderate role for IPH in the pathogenesis of neurologic events, it must be inter-
preted far more cautiously, with considerations given to various potential sources of heterogeneity and confounders.76

First, diverse methods of definition could introduce a tremendous amount of variability in the detection of IPH. As early as the 1980s, Fisher et al77 noted that it was dangerous to pool data, particularly when the analytical methods were different. Microscopy tended to be more sensitive for detecting IPH than macroscopy (49.2% and 33.8% here, respectively). Gross inspection was usually susceptible to subjective judgment, and there might be some misleading pathologic findings at the time of endarterectomy.20,26 Small or tiny hemorrhages could be overlooked as well. Moreover, we, along with Lovett et al,78 found that histologic methods including position, plane, number, stains, and frequency of section varied greatly. Therefore, a clear and uniform definition of IPH is necessary.

Second, there was evidence of inaccuracy, inconsistency, and inadequacy in the criteria of evaluation across studies. Age of the IPH could not be precisely defined by gross examination. A consensus on the histologic criteria used to assess IPH age was still lacking. Therefore, it is possible to discount an association between the time of occurrence of IPH and the onset of symptoms. Moreover, we, along with Lovett et al,78 found that histologic methods including position, plane, number, stains, and frequency of section varied greatly. Therefore, a clear and uniform definition of IPH is necessary.

Third, another possible explanation for heterogeneity could be identified as the variable interval between the latest onset of ischemia and histologic examinations after carotid endarterectomy. Lusby et al7 suggested a short interval (2.9 weeks, median) as a key factor in establishing a positive correlation. However, our review included studies with intervals ranging from a few days7 to 1 year or more.9 Acute IPH and concomitant plaque rupture with associated cerebral ischemia could be organized and stabilized by a process of healing or turning into an avascular structure (eg, fibrous or calcified tissues) with time. Therefore, the longer the interval between symptom onset and surgery is, the lower the expected incidence of IPH would be. As a consequence, it could partly explain the fact that the reported incidence of IPH varied widely from 1 study to another.

Fourth, the influence of IPH might also vary over time as social and economic factors change. The strongest associations were found in studies during the 1980s.7,13,66,67 Data from the mid-1990s and onward emerged on the beneficial effects of statins in the prevention of coronary heart disease.79 Because cholesterol-lowering therapy might reduce risks of ischemic heart disease as well as extracranial and intracranial atherosclerosis, studies were accordingly dichotomized at 1995. Studies published after 1995 showed an insignificant effect and were marginally free of the problem of heterogeneity, whereas earlier reports (before 1995) showed greater heterogeneity. The introduction of preventive treatment could have attenuated the penetrance of cerebrovascular symptoms, particularly for those patients with IPH. Alternatively, other possible explanations for diminished effects and mitigated heterogeneity might be due to improved methods of evaluation, high-quality design, and greater control of confounders. Therefore, the effect might be multifactorial instead of having been caused by statin treatment alone.

Fifth, carotid stenosis severity related to both IPH (exposure) and neurologic symptoms (disease) under study could strongly distort the results. A positive association between the presence of hemorrhages and critical stenosis was previously

Assessment of publication bias with the funnel plot, which reveals a curious asymmetry.
emphasized in 12 studies. It appeared that IPH represents an index of stenosis severity. However, a majority of studies (except for 8) did not determine whether patients with high-grade stenoses were proportionately distributed in each group. The collected data on the degree of stenosis posed further problems because diagnostic instruments and criteria have changed over time. To correct for this confounding, Golledge et al performed a summation calculation among studies with patients with equal stenosis severity. Their report demonstrated that IPHs were equally common in symptomatic and asymptomatic patients. We observed similar results from our meta-analysis. The problem of heterogeneity was totally mitigated, compared with the substantial heterogeneity that was still found among the remaining studies. Because estimated effects and significant heterogeneity are essentially influenced by the extent of disease, it is strongly recommended that equal disease severity in both groups should be assumed in the subsequent studies.

Finally, in addition to the 6 quality criteria, there were still several methodologic issues that could potentially affect the strength of association. Patient selection played a major role (selection bias). As shown in a number of studies, endarterectomy was selectively performed for higher-grade asymptomatic carotid stenoses compared with symptomatic stenoses. Ischemic manifestations were defined diversely across studies. Usually asymptomatic patients were defined as those who had never experienced a focal symptom on the side of interest, whereas patients with a remote history of symptoms or postmortem specimens were also considered asymptomatic. Patients with nonhemispheric symptoms (eg, hemianopia, dysarthria, and syncope) were sometimes either combined with asymptomatic patients into a control group or were combined with symptomatic patients into the exposed group. The choice of control group (whether patients were truly asymptomatic or had fleeting symptoms that could not be simply recalled) was likely to affect the magnitude of the association. As for risk factors, few studies specified that they were equally distributed in both groups; however, it was reported that systematic hypertension was positively correlated with the presence of IPH.

It should be noted there was some evidence that IPH was less important in the production of neurologic deficits. For example, a higher incidence of hemorrhage in asymptomatic groups was reported. More than half of the included studies showed no significant increase in symptoms based on IPH. Our findings indicate that studies with minor heterogeneity and high quality tended to yield negative results. A null association was also found in 2 studies with the largest sizes. Because studies mostly failed to take account of the subtypes of IPH and did not fully control the confounders, it was very difficult to accurately assess a role for IPH in the risk of symptoms. Considering the discouraging high heterogeneity, speculation might be premature and the causality of association might be less informative. Of note, a suspicious asymmetry of funnel plots was observed, and an inconsistency was found among related formal testing. The effect might be overestimated. Moreover, IPH rarely occurred without ulceration and was closely related to the presence of ulceration. Hence, IPH sometimes might not be a separate entity per se. This could potentially prevent IPH from being an independent risk factor for neurologic events. Therefore, we were unable to precisely estimate the contribution of the hemorrhage to neurologic events. A large, prospective, well-conducted study with a comprehensive and uniform evaluation might be warranted.

In addition, a summation analysis among 4 studies suggested that the incidence of IPH was not significantly different between asymptomatic and transiently symptomatic groups (32.5% versus 31.2%; P = 0.632). However, there was a salient trend of more IPHs in the prior stroke group compared with the asymptomatic group (43.8% versus 32.5%; P = 0.003). When these findings were subjected to a meta-analysis, borderline significance was observed (OR = 1.41, 95% CI, 1.02 to 1.95, P = 0.04; heterogeneity, P = 0.79). It indicated that the pathogenetic role of IPH might differ between patients with transient events and those with permanent neurologic deficits.

There are several noteworthy drawbacks to this review. Individual studies were mostly hospital based, which could potentially prevent extrapolating our results to the general population. Second, basic data, such as the number of IPHs in exposed and nonexposed groups, were not provided by many of the relevant studies. A majority of investigations were validation studies that compared in vivo imaging with histology. Third, no quantitative assessment of potential sources leading to the occurrence of major heterogeneity could be made, given the lack of specific data on these confounders. Finally, the influence of IPH on the risk of symptoms might vary in different ethnicities. Unfortunately, we were unable to assess their role and to what degree they influenced our results.

**Summary**

The current systematic review was designed to provide statistical evidence on the association between IPH and clinical symptoms. Overall, statistical findings suggested a plausible contribution of IPH to symptom production, but there was a devastating trend in heterogeneity between studies, with a much stronger association in small, early (before 1995), microscopic, methodologically less rigorous studies as well as studies with unequal extent of disease. Heterogeneity was weakened among studies of high quality, large size, recent reports (after 1995), and equal extent of disease. IPH was defined with great variation across studies. Speculation about an underlying association might be inconclusive because of a lack of control of confounders. A large, well-conducted study with uniform evaluation might be warranted.

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Disclosures

None.

References


Correlation Between Carotid Intraplaque Hemorrhage and Clinical Symptoms: Systematic Review of Observational Studies
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