Complex Atheromatous Plaques in the Descending Aorta and the Risk of Stroke
A Systematic Review and Meta-Analysis

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Background and Purpose—Proximal aortic plaques, especially in the aortic arch, have already been established as an important cause of stroke and peripheral embolism. However, aortic plaques situated in the descending thoracic aorta have recently been postulated as a potential embolic source in patients with cryptogenic cerebral infarction through retrograde aortic flow. The aim of the present study was to evaluate the potential association of descending aorta atheromatosis with cerebral ischemia.

Methods—We conducted a systematic review and meta-analysis of all available prospective observational studies reporting the prevalence of complex atheromatous plaques in the descending aorta in patients with stroke and in unselected populations undergoing examination with transesophageal echocardiography.

Results—We identified 11 eligible studies including a total of 4000 patients (667 patients with stroke and 3333 unselected individuals; mean age, 65 years; 55% men). On baseline transesophageal echocardiographic examination, the prevalence of complex atheromatous plaques in the descending aorta was higher (P=0.001) in patients with stroke (25.4%; 95% confidence interval, 14.6–40.4%) compared with unselected individuals (6.1%; 95% confidence interval, 3.4–10%). However, no significant difference (P=0.059) in the prevalence of complex atheromatous plaques in the descending aorta was found between patients with cryptogenic (21.8%; 95% confidence interval, 17.5–26.9%) and unclassified (28.3%; 95% confidence interval, 23.9–33.1%) cerebral infarction.

Conclusions—Our findings indicate that the presence of complex plaques in the descending aorta is presumably a marker of generalized atherosclerosis and high vascular risk. The present analyses do not provide any further evidence for a direct causal relationship between descending aorta atherosclerosis and cerebral embolism. (Stroke. 2014;45:1764-1770.)

Key Words: aorta, thoracic ▪ atherosclerosis ▪ brain ischemia ▪ stroke

Approximately 1 in 4 patients with an embolic event is found to have variable grades of aortic atheromatosis in transesophageal echocardiography (TEE). Atherosclerotic lesions of the thoracic aorta, especially complex plaques with superimposed thrombi and thickness >4 mm, are thought to be a risk factor for both cerebral and peripheral embolization. Moreover, aortic plaques situated in the descending thoracic aorta are often overlooked and may be neglected as a potential mechanism of cerebral embolism through retrograde aortic flow. Interestingly, 3-dimensional and 4-dimensional MRI data via image fusion demonstrated that emboli from complex plaques in the descending aorta reached the left subclavian artery and common carotid artery in 67% and 25% of evaluated cases. In addition, retrograde embolism from the descending aorta was postulated as the only probable cause of retinal or cerebral infarction in 24% of patients with cryptogenic stroke.

The aim of the present systematic review and meta-analysis was to evaluate the potential association of atheromatosis in the descending aorta with cerebral ischemic events using data from prospective observational studies. We also estimated the prevalence of complex atheromatous plaques in the descending aorta in patients with unclassified ischemic stroke, cryptogenic infarction, and unselected individuals undergoing TEE examination for various indications.

Methods

Trial Identification and Data Abstraction
This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic
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reviews and meta-analyses. Eligible studies reporting the association of descending aortic atherosclerosis with stroke were identified by searching MEDLINE, SCOPUS, and the Cochrane Database of Systematic Reviews. The following combination of search strings was used in the literature search: (descending aorta atherosclerosis) AND cerebral ischemia) OR (descending aorta plaques) AND stroke. No language or other restrictions were imposed. Last literature search was conducted on January 30, 2014. Reference lists of all articles that met the criteria and of relevant review articles were examined to identify studies that may have been missed by the database search.

All retrieved studies from the aforementioned literature search were scanned by 2 independent reviewers (A.H.K. and G.T.) to include only prospective cohort studies that reported the prevalence of complex atheromatous plaques in the descending aorta after investigation with TEE. Atheromatous plaques in the descending aorta were defined as complex if they were protruding (>4 mm thick), ulcerated, or had mobile components (mobile debris). Retrospective cohort studies, case series, case reports, or studies reporting the prevalence of complex atheromatous plaques in the descending aorta after initial investigation with imaging methods other than TEE were excluded from the final analysis. Studies that did not investigate the prevalence of complex atheromatous plaques in the descending aorta were also excluded.

In each study that met the inclusion criteria, a predefined 9-point quality control, which was adapted from a recent systematic review on the prevalence of depression in chronic kidney disease by Palmer et al., was used to address biases. For each quality item, the corresponding risk of bias was categorized as low, high, or unclear according to the suggestions by H Higgins et al. Quality control and bias identification were performed by 2 independent reviewers (A.H.K. and G.T.), and all emerging conflicts were resolved by consensus. Data on the prevalence of complex atheromatous plaques in the descending aorta were extracted independently by the 2 authors who performed the literature search (A.H.K. and G.T.). After the overall analysis of all included studies, we dichotomized the retrieved prospective cohort studies, according to the population in whom TEE was initially performed, in 2 subgroups: stroke population TEE subgroup and unselected population TEE subgroup. We included in the stroke subgroup prospective studies that investigated patients after stroke or transient ischemic attack with TEE, whereas in the unselected subgroup, we included all those studies that prospectively reviewed all patients who underwent TEE for various reasons in a particular time period. Studies that included mixed patients with stroke, transient ischemic attack, and peripheral embolism were not included in neither subgroup and were excluded from the final analysis. In the stroke subgroup, we performed a subsequent subgroup analysis between patients with cryptogenic ischemic stroke and those with unclassified ischemic stroke on the prevalence of complex plaques in the descending aorta on the initial TEE examination. In the unclassified stroke subgroup, we included all those patients who were reported to have an ischemic stroke, which was not further classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Finally, we performed a post hoc subgroup analysis comparing demographic characteristics and vascular risk factors among patients with cryptogenic, unclassified ischemic infarction and unselected patients.

Statistical Analyses

We calculated the point prevalence in each study by dividing the number of events (prevalent complex plaques or baseline characteristics) by the total number of patients. Mean age in years, with the corresponding SD and sample size, was pooled across studies. The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, we used a random-effects model (DerSimonian–Laird) to combine studies within each subgroup and a fixed-effects model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance ($\tau^2$) to be the same for all subgroups. $\tau^2$ was first computed within subgroups and then pooled across subgroups. Heterogeneity between studies was assessed by the Cochran Q and $I^2$ statistic. For the qualitative interpretation of heterogeneity, $P$ values $\leq 50\%$ were considered to represent substantial heterogeneity, whereas values $\geq 75\%$ indicated considerable heterogeneity, according to the Cochrane Handbook. Publication bias was assessed at the overall analysis, to maximize the power of the test, with the Egger statistical test. All analyses were conducted using Comprehensive Meta-Analysis version 2 software.

Results

Study Selection and Study Characteristics

MEDLINE search yielded 94 results and SCOPUS search yielded 55 results. Excluding 32 duplicate studies, the remaining 117 studies were screened for eligibility. Potentially eligible studies for the meta-analysis (n=15) were retained, after screening both the titles and abstracts of all studies. After retrieving the full-text version of the aforementioned 15 studies, we excluded 3 studies because patients with stroke were mixed with patients with peripheral embolization, and 1 study because of its retrospective study protocol. The remaining 11 studies were included both in qualitative and in quantitative synthesis (Figure 1). The characteristics of included studies are summarized in Table 1.

Risk of Bias for Independent Studies

Risk of bias in the included studies is summarized in Figure 2. In 7 of 11 studies, consecutive patients were enrolled; in 1, a randomized sample from a large study cohort was selected; and in the remaining 3, no information was reported about the consecutiveness of study participants. In 3 of 10 studies, the study setting, including location and enrollment dates, or the inclusion criteria were not clearly stated in the articles. Excluding patients after recruitment was mentioned in 3 studies. Baseline characteristics and medications were not provided in 3 and 10 studies, respectively. TEE protocol was sufficiently presented in 10 studies, but blinding in imaging protocol from clinical data was reported only in 4 studies. Finally, a funding source was acknowledged in 4 studies. However, it should be noted that all funding sources were public institutional funding sources.

Overall Analysis and Subgroup Analysis

The point prevalence of complex atheromatous plaques in the descending aorta within the 11 individual study populations comprising 4000 participants (mean age, 65 years; 55% men) ranged between 2% and 32%. The mean prevalence of all pooled studies was 12% (95% confidence interval [CI], 8–18%) with evidence of high-level heterogeneity between estimates ($I^2=96.4\%$; $P<0.001$). No publication bias was evident in the funnel plots ($P=0.451$; Egger statistical test).

In subgroup analysis, complex atheromatous plaques in the descending aorta were more prevalent ($P=0.001$) in patients with stroke (25.4%; 95% CI, 14.6–40.4%) compared with unselected patients (6.1%; 95% CI, 3.4–10%) on baseline examination (Figure 3). The observed heterogeneity in trials with unselected patients was higher ($I^2=96.17\%$; $P<0.001$) in comparison with the heterogeneity detected in studies evaluating patients with stroke ($I^2=15.26\%$; $P=0.317$). In the subsequent subgroup analysis of 5 studies that included 667 patients with stroke (Figure 4), no significant difference ($P=0.059$) in the prevalence of complex atheromatous plaques...
in the descending aorta was found between the cryptogenic stroke subgroup (22%; 95% CI, 18–27%) and the unclassified stroke subgroup (28%; 95% CI, 24–33%). We detected no heterogeneity among estimates from different studies including patients with stroke ($I^2=15.26\%$; $P=0.317$). Post hoc subgroup analysis revealed nonsignificant differences in demographic characteristics and vascular risk factors between patients with cryptogenic stroke and those with unclassified ischemic stroke, or between patients with stroke and unselected patients (Table 2). Notably, patients with cryptogenic cerebral infarction tended to be younger (mean age, 57 years) than patients with unclassified ischemic stroke (mean age, 67 years; $P=0.213$). Moreover, patients with stroke tended to have a greater prevalence of diabetes mellitus (mean, 24.4%) compared with unselected patients (mean, 14.7%; $P=0.143$).

**Discussion**

To the best of our knowledge, this is the first systematic attempt to summarize and evaluate meta-analytically the existing literature about the potential association of complex atheromatous plaques in the descending aorta and ischemic stroke. Our findings indicate that complex atheromatous plaques in the descending aorta are $\approx 4\times$ more prevalent in patients with stroke undergoing TEE compared with unselected patients who undergo TEE for various reasons. Among patients with stroke, those with cryptogenic stroke tended to have a lower

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study Population</th>
<th>n</th>
<th>Imaging Method</th>
<th>Total Plaques</th>
<th>Complex Plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amarenco et al13</td>
<td>1994</td>
<td>France</td>
<td>IS</td>
<td>250</td>
<td>TEE</td>
<td>250</td>
<td>72</td>
</tr>
<tr>
<td>Chatzikonstantinou et al16</td>
<td>2012</td>
<td>Germany</td>
<td>CS</td>
<td>64</td>
<td>TEE/CTA</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Gu et al17</td>
<td>2011</td>
<td>United States</td>
<td>CS</td>
<td>229</td>
<td>TEE</td>
<td>...</td>
<td>50</td>
</tr>
<tr>
<td>Harloff et al15</td>
<td>2008</td>
<td>Germany</td>
<td>IS</td>
<td>74</td>
<td>TEE/MRI</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Matsumura et al14</td>
<td>2002</td>
<td>Japan</td>
<td>IS</td>
<td>50</td>
<td>TEE</td>
<td>...</td>
<td>16</td>
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<tr>
<td>Agmon et al18</td>
<td>2002</td>
<td>United States</td>
<td>Unselected</td>
<td>581</td>
<td>TEE</td>
<td>261</td>
<td>35</td>
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<td>Ferrari et al23</td>
<td>1999</td>
<td>France</td>
<td>Unselected</td>
<td>1,116</td>
<td>TEE</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Haruki et al23</td>
<td>2010</td>
<td>Japan</td>
<td>Unselected</td>
<td>350</td>
<td>TEE</td>
<td>170</td>
<td>51</td>
</tr>
<tr>
<td>Karalis et al21</td>
<td>1991</td>
<td>United States</td>
<td>Unselected</td>
<td>556</td>
<td>TEE</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Russo et al19</td>
<td>2009</td>
<td>United States</td>
<td>Unselected</td>
<td>209</td>
<td>TEE</td>
<td>126</td>
<td>41</td>
</tr>
<tr>
<td>Tunick et al22</td>
<td>1994</td>
<td>United States</td>
<td>Unselected</td>
<td>521</td>
<td>TEE</td>
<td>...</td>
<td>27</td>
</tr>
</tbody>
</table>

CS indicates cryptogenic stroke; CTA, computed tomographic angiography; IS, ischemic stroke; and TEE, transesophageal echocardiography.
prevalence of atheromatous plaques in the descending aorta when compared with patients with stroke with unclassified stroke. In subsequent post hoc subgroup analysis, patients with cryptogenic stroke and those with unclassified stroke did not differ in terms of demographic characteristics and vascular risk factors.

Aortic plaques are considered a marker of generalized atherosclerosis, and thus the presence of aortic plaques could be considered a sufficient but not a necessary condition to prove that a patient has a systemic atherosclerotic disease. Aortic atheromatous plaques are more frequently found in elders, smokers, and in patients with hypertension, diabetes mellitus, or hypercholesterolemia.3 The presence of plaques in the aorta was found to be significantly associated with both intracranial and extracranial atherosclerosis in patients with stroke,24 whereas plaques in the arch and descending aorta were found

Figure 2. Risk of bias in individual studies that were included for meta-analysis (low risk=bias, if present, is unlikely to alter the results seriously; unclear risk=a risk of bias that raises some doubt about the results; high risk=bias may alter the results seriously).

Figure 3. Prevalence of complex atheromatous plaques in the descending aorta. CI indicates confidence interval.
to be an independent predictor of >70% extracranial carotid artery stenosis in patients with stroke or transient ischemic attack.\textsuperscript{22} Age, smoking history, and pulse pressure were independently associated with a higher frequency of atherosclerosis and complex atherosclerosis in the aorta.\textsuperscript{18} Increasing age was not only associated with plaque complexity in all aortic segments,\textsuperscript{20} but particularly with increasing plaque thickness in both the aortic arch and the descending aorta.\textsuperscript{19} Aortic plaques are mainly observed, with almost the same frequency, in the aortic arch and the descending aorta, probably because of the tortuous S-shaped blood flow in these segments of the aorta.\textsuperscript{5,26} Thickness of plaques in the aortic arch was found to be significantly correlated with plaque thickness in the descending aorta.\textsuperscript{27} Additionally, the presence of atheromatous plaques in the aortic arch, but not in the descending aorta, was found to be correlated with increased reversal of blood flow in the aortic arch.\textsuperscript{26}

Retrograde flow from the descending aorta has been found to be frequent in patients with determined or cryptogenic stroke\textsuperscript{6} and in patients with uncomplicated hypertension.\textsuperscript{28} Flow reversal in the descending aorta was found to increase with increasing age,\textsuperscript{29} decreasing heart rate,\textsuperscript{4} increasing aortic stiffness,\textsuperscript{28} and the presence of complex plaques,\textsuperscript{6} which also in turn affect aortic elasticity.\textsuperscript{3} Interestingly, aortic valve insufficiency and aortic regurgitation were not found to be significant predictors of increased flow reversal.\textsuperscript{29,30} In view of the former considerations, retrograde embolization from complex plaques of the proximal descending aorta to all brain territories in early diastole is theoretically possible and could provide an alternative embolic source that should be taken into consideration, especially in patients with cryptogenic stroke.\textsuperscript{6,28,30,31}

However, in a small, prospective, population-based study, neither complex nor small plaques in the descending aorta were associated with an increased risk of first-ever stroke after a mean follow-up of 74.4 months. Moreover, subjects with large plaques in the descending aorta were also found to have a higher prevalence of hypertension, diabetes mellitus, and hypercholesterolemia, when compared with those without plaques.\textsuperscript{19} Moreover, the only available evidence in literature about the potential association of complex atheromatous plaques in the descending aorta with recurrent stroke is a case report of a 69-year-old white woman who experienced recurrent posterior circulation embolic strokes attributed to a large complex ulcerated atheromatous plaque in the proximal

**Figure 4.** Prevalence of complex atheromatous plaques in the descending aorta in patients with cerebral ischemia. CI indicates confidence interval.

**Table 2.** Pooled Cardiovascular Risk Factors From the Baseline Characteristics Across Studies Reporting Complex Atheromatous Plaques in Patients With Cryptogenic Stroke or Nonclassified Cerebral Ischemia

<table>
<thead>
<tr>
<th>Baseline Risk Factor</th>
<th>Cryptogenic Stroke</th>
<th>Unclassified Ischemic Stroke</th>
<th>(P) Values</th>
<th>Overall Stroke</th>
<th>Unselected Patients</th>
<th>(P) Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.7 (44.3–69.1)</td>
<td>66.8 (56.7–76.9)</td>
<td>0.213*</td>
<td>62.8 (56.3–69.3)</td>
<td>68.5 (60.3–76.8)</td>
<td>0.285*</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>58.5 (36.6–77.5)</td>
<td>56.7 (38.6–73.2)</td>
<td>0.902*</td>
<td>55.8 (47.6–63.3)</td>
<td>54.6 (45.3–63.5)</td>
<td>0.848*</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>70.1 (49.6–84.8)</td>
<td>59.5 (41.8–75.0)</td>
<td>0.663*</td>
<td>64.2 (54.5–72.9)</td>
<td>64.4 (57.0–71.1)</td>
<td>0.951*</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>37.2 (24.8–51.5)</td>
<td>27.7 (18.7–38.9)</td>
<td>0.269*</td>
<td>31.4 (22.7–41.7)</td>
<td>37.6 (23.9–53.5)</td>
<td>0.496*</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30.9 (20.5–43.6)</td>
<td>20.1 (13.5–28.9)</td>
<td>0.123*</td>
<td>24.4 (15.9–34.5)</td>
<td>14.7 (8.5–24.4)</td>
<td>0.143*</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>38.0 (31.6–44.8)</td>
<td>38.7 (33.6–44.0)</td>
<td>0.873</td>
<td>36.4 (21.1–55.5)</td>
<td>34.1 (18–54.9)</td>
<td>0.862*</td>
</tr>
</tbody>
</table>

All analyses were performed from the available point estimates using the mixed effects model. \(\tau^2\) was first computed within subgroups and then pooled across subgroups. The results of the subgroup analyses for each risk factor are presented as point estimates with their corresponding 95% confidence intervals in parentheses.

*Considerable heterogeneity was found in the within-studies analysis.

†Available data in 4 studies.
descending aorta found on both computed tomographic angiography and TEE. The present findings lend support to the assumption that complex atheromatous plaques in the descending aorta may be more prevalent in patients with stroke as an indicator of generalized atherosclerosis, but do not seem to be related to cerebral embolism in patients with cryptogenic stroke. Interestingly, our findings indicate that patients with stroke with complex plaques in the descending aorta tended to have a higher prevalence (9.7%) of diabetes mellitus in comparison with unselected patients with descending aortic plaques in TEE evaluation. According to the above, the mechanism of retrograde cerebral embolization from descending aortic atheroma still remains on a hypothetical basis, and just the visualization of descending aortic atheroma on TEE or computed tomographic angiography/magnetic resonance angiography should be considered an additional finding, and not a definitive finding. Certain limitations of this report need to be acknowledged. First, we excluded studies reporting initial investigation of the descending aorta with imaging modalities other than TEE. In previous decades, radiological imaging techniques were not developed sufficiently, and thus protruding and mobile atheromas in the aortic arch and the descending aorta that were visualized by TEE may have been missed by other radiological techniques including angiography and computerized tomography. Even in a recent comparative study, computed tomographic angiography was found to have 53% sensitivity and 89% specificity in detecting aortic arch atheromas compared with TEE. Although MRI and computed tomographic angiography are now emerging as powerful noninvasive tools, TEE still remains the gold standard and the first choice for screening aortic atheromas. Second, studies that did not provide a prevalence estimate of complex atheromatous plaques in the descending aorta and the studies reporting mixed groups of patients with embolism (stroke, transient ischemic attack, or peripheral embolism) were also excluded. Third, although publication bias was not detected, there is evidence of high risk for detection bias because only 34.6% of individual studies reported a blinding method in their imaging protocol. Selection bias could also be probable in studies that enrolled nonconsecutive or nonrandomized patients and in those studies that did not report distinctly the inclusion criteria or excluded patients after initial recruitment. An additional cause for possible selection bias and false prevalence rates in the individual studies with patients with stroke is that not all patients with stroke (and even those with cryptogenic stroke) undergo TEE. The presence of all these biases could partially result in the substantial heterogeneity that was mainly observed between studies of unselected populations. Moreover, data on the prevalence of coronary artery disease were presented in only 3 of 5 available studies, and consequently, this risk factor was not included in our analyses. Last and most important, the present review cannot evaluate a causal relationship between atheromatous plaques in the descending aorta and cerebral ischemia that should further be investigated in prospective cohort studies.

In conclusion, the present systematic review and meta-analysis showed that patients with stroke have a 4-fold higher prevalence of complex atheromatous plaques in the descending aorta compared with unselected individuals. However, the prevalence of complex atheromatous plaques in the descending aorta did not differ between patients with cryptogenic ischemic stroke and patients with unclassified cerebral ischemia. Consequently, it may be postulated that the presence of complex plaques in the descending aorta may constitute a marker of generalized atherosclerosis and high vascular risk, but cannot be causally related with a higher risk of cryptogenic ischemic stroke.

Sources of Funding

Dr Tsivgoulis has been supported by European Regional Development Fund, Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Disclosures

None.

References

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Stroke. 2014;45:1764-1770; originally published online May 1, 2014;
doi: 10.1161/STROKEAHA.114.005190
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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