Effect of Aspirin and Warfarin Therapy in Stroke Patients With Valvular Strands

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Background—Valvular strands are associated with ischemic stroke. The recurrent rate of adverse events in stroke patients with valvular strands has not been defined and, importantly, there are no randomized studies to evaluate efficacy of antithrombotic therapies in these patients.

Methods—Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) enrolled 630 stroke patients, of whom 312 (49.5%) were randomized to warfarin and 318 (50.5%) were randomized to aspirin; 265 patients experienced cryptogenic stroke and 365 experienced stroke with known subtypes. Endpoints were recurrent ischemic stroke or death from any cause. All transesophageal echocardiography studies were blindly, centrally analyzed and all endpoints were blindly adjudicated.

Results—Overall, of 619 studies analyzed, valvular strands were present in 39.4% of the patients (244/619), 5.8% (36/619) on the aortic valve and 27.8% (172/619) on the mitral valve, and 5.8% (36/619) on both valves. In an intention-to-treat analysis, there was no significant difference in the time to primary endpoints between patients with and without strands in the overall population (P=0.82; hazard ratio: 1.05; 95% CI: 0.70 to 1.57; 2-year event rates: 16.4% versus 15.5%). Among the patients with strands, there was no significant difference in the time to primary endpoints between those treated with warfarin or aspirin (P=0.21; hazard ratio: 0.67; 95% CI: 0.36 to 1.26; 2-year event rates: 13.5% versus 19.6%).

Conclusions—While on medical therapy, valvular strands do not significantly increase recurrent adverse event rates in patients with ischemic stroke. Furthermore, the study does not provide evidence to support an advantage of warfarin or aspirin for this purpose. (Stroke. 2004;35:1436-1442.)

Key Words: stroke • echocardiography • epidemiology • mitral valve • aortic valve

Valvular strands are filiform material attached to the cardiac valve edges detected by transesophageal echocardiography (TE) that have been associated with stroke.1–5 Lee reported that 11 of 50 patients with presumed cerebral embolic event had filamentous strands on the mitral valve.1 Freedberg found that 10.6% of the patients with embolic events had strands compared with 2.3% in those without such events.2 Tice reported that mitral valve strands were found in 6.3% of those undergoing TE as a result of a recent cerebral ischemic event compared with the 0.3% prevalence in patients referred for other indications.3 We have previously reported that strands were found more frequently in stroke patients compared with controls. This risk was found to be greater for younger patients in whom the finding of valvular strands was infrequent.4

However, the optimal treatment modality to prevent recurrent events in patients with valvular strands has not been studied. Aspirin and warfarin are the most commonly used, but there are no data on the efficacy of any of the treatment options. The single study addressing this issue was observational without treatment randomization.5 Accordingly, from the data obtained in the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), we sought to define the adverse event rate in stroke patients with valvular strands on mitral and aortic valve, double-blindly randomly assigned to warfarin or aspirin.

Patients and Methods

Patient Recruitment

PICSS relied on the Warfarin-Aspirin Recurrent Stroke Study (WARSS: NIH RO1-NS-28371; J.P. Mohr, Principal Investigator) for patient recruitment and follow-up. WARSS was a 48-center double-blind study that randomized 2206 stroke patients to either warfarin or aspirin and then followed them for stroke recurrence or death over a 24-month period.5,7 Patient recruitment started in June 1993 and follow-up was completed in June 2000. At each center, cryptogenic stroke patients in WARSS were solicited to undergo TE. PICCS also included in all WARSS patients who underwent TE for clinical purposes. PICCS patients were therefore a subset of patients.
in WARSS and included cryptogenic stroke patients and patients with other stroke subtypes. All protocols for WARSS and PICSS were approved by the Institutional Review Board at each participating center and informed consent was obtained from each participant.

**Eligibility**
Patients aged 30 to 85 deemed safe to undergo warfarin therapy were eligible. Eligible patients experienced ischemic stroke within the previous 30 days and were rated ≥3 on the Glasgow Outcome Scale (severe disability, moderate disability, no or minimal disability). Ineligible patients had baseline international normalized ratio (INR) above normal range (>1.4), stroke related to a procedure, attributable to major cardioembolic source, or planned to undergo surgery for high-grade carotid stenosis. Patients with contraindications to TE were excluded from consideration for participation in PICSS.

**Stroke Subtyping**
All baseline strokes were subtyped by a local neurology principal investigator (PI) based on a predefined criteria modeled after the National Institute of Neurological Diseases and Stroke (NINDS) Stroke Data Bank and Trial of Organon in Acute Stroke Therapy (TOAST). Subtypes were lacunar, large vessel, cryptogenic, other determined cause, and conflicting mechanisms. Lacunar infarcts showed brain imaging evidence of a small, deep infarct and no source of cardioembolism. Large-vessel atherosclerosis required evidence of extracranial or intracranial occlusion or moderate to severe stenosis of the carotid, vertebral, middle cerebral, or basilar arteries. Cryptogenic stroke typically had no definite source of the stroke despite a thorough diagnostic evaluation.

**Medications and Blinding**
Medications used were aspirin 325-mg tablets taken once daily and warfarin taken daily, adjusted to achieve and maintain INR 1.4 to 2.8. Patients were randomized to active aspirin or warfarin and an identical placebo. All patients followed the same schedule of clinic contacts for blood draws for INR, medication monitoring, and warfarin (or warfarin-dummy) dose-adjustment. All participants other than the principal statistician were blinded.

**Follow-Up**
All patients were followed-up for 2 years, operationally defined as 24±1 month (maximum 761 days). Follow-up was performed on a regular basis by phone and in person to assess compliance and to regulate INRs. Quarterly and annual in-person follow-ups for detailed examination were also made.

**TE Protocol**
All patients underwent TE guided by a predefined PICSS protocol using either a biplane or a multiplane TE probe, and the videotapes were sent to Columbia University (NY) for central analysis. The TE protocol emphasized delineation of TE-associated embolic sources, including characterization of valvular strands. Ongoing quality control was monitored with feedback to the site regarding TE study quality.

**Analysis of Tapes**
All TE tapes were analyzed by a single observer (S.H.). Valvular strand was defined as thin filamentous material ≤1 mm in thickness and extending for ≥2 mm from the edges of mitral or aortic valve, into the left atrium at systole for the mitral valve, and into the left ventricle at diastole for the aortic valve.

**Assessment of Endpoints**
The primary endpoint was clinically evident recurrent ischemic stroke or death from any cause. Clinical evidence of a recurrent ischemic stroke was a new lesion on CT or MRI or when new lesions were absent and clinical syndrome consistent with stroke with duration >24 hours. All clinical and radiological events were adjudicated independently. All hemorrhages were adjudicated by a treatment-blinded adjudicator. Definition of major and minor hemorrhages are presented elsewhere.

**Statistical Analysis**
The primary null hypothesis was that the presence or absence of valvular strands did not affect the time to recurrent ischemic stroke or death from any cause in patients treated with either warfarin or aspirin. Secondary null hypotheses were that strand location did not affect the time to primary endpoint, that treatment with either warfarin or aspirin did not differentially affect the time to primary endpoint, and that the presence of strands did not affect the time to primary endpoint or transient ischemic attack (TIA).

Kaplan-Meier curves were constructed and a log-rank test was used to compare curves for those with and without valvular strands. A Cox proportional hazards model was used to determine the relative hazards ratio and associated confidence interval. Similar analyses were performed for secondary hypotheses. Reported 2-year event rates are estimates obtained from the Kaplan-Meier curves that adjust for censoring. \( P<0.05 \) was considered significant for all analyses.

**Results**
During the recruitment phase, 630 patients were randomized at a steady rate. After the planned 2 years of follow-up, endpoint status was known for 620 (98.4%) patients. The remaining 10 (1.6%) withdrew consent or were lost to follow-up at a mean 13.2±10.5 months after randomization. Of the 2206 patients enrolled and randomized in WARSS, 630 (28.6%) were enrolled in PICSS. When the strokes were subtyped, 265 (42.1%) were cryptogenic, 244 (38.7%) lacunar, 68 (10.8%) large vessel, 27 (4.3%) other determined cause, and 26 (4.1%) conflicting mechanism.

**Laboratory Testing**
Of 630 patients, 312 (49.5%) were randomized to warfarin and 318 (50.5%) to aspirin. The mean INR in the warfarin-treated patients was 2.04±0.99 (median 1.86), with a mean time interval between blood draws of 28.1±13.4 days. For warfarin-treated patients with valvular strands, the mean INR was 2.11±0.90 (median 1.93) and for warfarin-treated patients without valvular strands, the mean INR was 1.99±0.98 (median 1.83).

**Baseline TE Findings**
Of 630 patients, TE studies were available for analysis in 627. Of these, 619 (98.7%) had TE images adequate for analysis of valvular strands. Valvular strands were present in 244 (39.4%) of the patients, of which 5.8% (36/619) were on aortic valve, 27.8% (172/619) on mitral valve, and 5.8% (36/619) on both valves. Characteristics of patients with and without valvular strands are shown in Table 1. Valvular strands were found in 38.6% (101/262) of patients with cryptogenic stroke compared with 40.1% (143/357) in patients with known cause of stroke (\( P=NS \)).

**Endpoints**
The analyses were adjusted for the 10 patients lost to follow-up using a prespecified imputation procedure stratified by an independent observer for the different types of those lost to follow-up. Using this model, the overall primary event rate was 15.9%. Among the 619 patients with adequate TE images for valvular strand analysis, there was a total of 99 endpoints (16.0%); 72 strokes and 27 deaths occurred. Addi-
Additionally, 37 TIAs occurred, including 8 that occurred before the primary event. The number of patients with at least 1 major hemorrhage within 2 years was similar between those assigned to warfarin and aspirin (2.24% and 3.14%).

Primary Events in Relation to Valvular Strand Status

Presence of Valvular Strands
For the entire group, there was no significant difference in the time to recurrent stroke or death between those with and without valvular strands ($P=0.82$; hazard ratio: 1.05; 95% CI: 0.70 to 1.57; 2-year event rates: 16.4% versus 15.5%). Kaplan-Meier curves are shown as Figure. In the cryptogenic stroke group, there also was no significant difference in the time to primary events ($P=0.47$; hazard ratio: 1.28; 95% CI: 0.65 to 2.53; 2-year event rates: 15.0% versus 11.9%).

Location of Valvular Strands
The effect of valvular strand location on outcome is demonstrated in Table 2A. There was no significant difference in the time to stroke recurrence or death among those with and without valvular strands on aortic, mitral, or both valves when compared with those without strands. This was the case when TIA was considered to be an additional endpoint (Table 2B). When cryptogenic stroke patients were considered separately, there was no significant difference with and without inclusion of TIA as an endpoint (Tables 2C, 2D).

Treatment With Warfarin or Aspirin
As shown in Table 3A, when the groups with and without valvular strands were analyzed in relation to the efficacy of warfarin or aspirin, no significant differences were found for the time to primary events. This was the case when TIA was considered to be an additional endpoint (Table 3B). When cryptogenic stroke patients were considered separately, there was no significant difference with and without inclusion of TIA as an endpoint (Table 3C, 3D).

TABLE 1. Sociodemographic Variables, Stroke Characteristics, and Risk Factors of Patients With and Without Valvular Strands

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Group N=619 (%)</th>
<th>Strands N=244 (%)</th>
<th>No Strands N=375 (%)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59.2±12.2</td>
<td>59.0±12.6</td>
<td>59.3±11.9</td>
<td>0.77</td>
</tr>
<tr>
<td>Male</td>
<td>343/619 (55.4)</td>
<td>145/244 (59.4)</td>
<td>198/375 (52.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Race/ethnicity (White)</td>
<td>276/619 (44.6)</td>
<td>97/244 (39.8)</td>
<td>179/375 (47.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Married</td>
<td>337/617 (54.6)</td>
<td>131/244 (53.7)</td>
<td>206/373 (55.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>College educated</td>
<td>167/610 (27.4)</td>
<td>73/240 (30.4)</td>
<td>94/370 (25.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Medicaid</td>
<td>187/614 (30.5)</td>
<td>83/242 (34.3)</td>
<td>104/372 (28.0)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Stroke characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic subtype</td>
<td>286/619 (46.2)</td>
<td>111/244 (45.5)</td>
<td>175/375 (46.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Glasgow Score &lt;5</td>
<td>209/619 (33.8)</td>
<td>80/244 (32.8)</td>
<td>129/375 (34.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Barthel Score &lt;95</td>
<td>168/619 (27.1)</td>
<td>60/244 (24.6)</td>
<td>108/375 (28.8)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>317/612 (60.6)</td>
<td>144/239 (60.3)</td>
<td>227/373 (60.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>178/617 (28.8)</td>
<td>70/243 (28.8)</td>
<td>108/374 (28.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sedentary</td>
<td>217/614 (35.3)</td>
<td>88/241 (36.5)</td>
<td>129/373 (34.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Heart disease</td>
<td>120/619 (19.4)</td>
<td>48/244 (19.7)</td>
<td>72/375 (19.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>83/576 (14.4)</td>
<td>32/229 (14.0)</td>
<td>51/347 (14.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Current smoker</td>
<td>399/616 (28.9)</td>
<td>75/242 (31.0)</td>
<td>123/374 (27.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Heavy alcohol consumption</td>
<td>72/616 (11.7)</td>
<td>27/243 (11.1)</td>
<td>45/373 (12.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>241/616 (39.1)</td>
<td>104/243 (42.8)</td>
<td>137/373 (36.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Obese</td>
<td>303/614 (49.4)</td>
<td>112/241 (46.5)</td>
<td>191/373 (51.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>BMI</td>
<td>28.5±5.9</td>
<td>28.1±5.3</td>
<td>28.7±6.2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. *Valvular strands present vs absent.
Several reports have demonstrated the association between valvular strands and stroke, particularly in younger patients.1–4 Valvular strands are thought to represent Lambl ex crescences, which are a filiform structure initially identified on aortic valve by Lambl and then by Magarey on the aortic valve.10–12 Typically, strands can only be detected in vivo by TE. They are thought to form because of “wear and tear” of the valve, associated with fibrin deposition over damaged endocardial valvular surfaces that subsequently become partially detached from the valve, condensed, hyalinized, and ultimately fibrosed. When these structures be-

**TABLE 2A. Two-Year Rates of Recurrent Stroke or Death in Patients With Valvular Strands Depending on Strand Location**

<table>
<thead>
<tr>
<th></th>
<th>No Strand (N=375)</th>
<th>Any Strand (N=244)</th>
<th>Only Aortic Strand (N=36)</th>
<th>Only Mitral Strand (N=172)</th>
<th>Both Aortic and Mitral Strands (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>15.5</td>
<td>16.4</td>
<td>25.0</td>
<td>15.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Events</td>
<td>43S/16D</td>
<td>29S/11D</td>
<td>6S/3D</td>
<td>19S/7D</td>
<td>4S/1D</td>
</tr>
</tbody>
</table>

For Tables 2A–2D, S indicates stroke; T, transient ischemic attack; D, death. Hazard ratio aortic valvular strand = 1.73; 95% CI: 0.86–3.50; P = 0.12. Hazard ratio mitral valvular strand = 0.97; 95% CI: 0.61–1.54; P = 0.90. Hazard ratio both aortic and mitral valvular strands = 0.88; 95% CI: 0.35–2.19; P = 0.78.

*Event rates are calculated from Kaplan-Meier curves at 2 years. Hazard ratios are calculated with no valvular strands as the reference group.

**TABLE 2B. Two-Year Rates of Recurrent Stroke, TIA, or Death in Patients With Valvular Strands Depending on Strand Location**

<table>
<thead>
<tr>
<th></th>
<th>No Strand (N=375)</th>
<th>Any Strand (N=244)</th>
<th>Only Aortic Strand (N=36)</th>
<th>Only Mitral Strand (N=172)</th>
<th>Both Aortic and Mitral Strands (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>19.8</td>
<td>21.4</td>
<td>25.0</td>
<td>22.0</td>
<td>16.7</td>
</tr>
<tr>
<td>Events</td>
<td>39S/22T/15D</td>
<td>27S/15T/10D</td>
<td>6S/0T/3D</td>
<td>17S/14T/6D</td>
<td>4S/1T/1D</td>
</tr>
</tbody>
</table>

Hazard ratio aortic valvular strand = 1.31; 95% CI: 0.66–2.62; P = 0.44. Hazard ratio mitral valvular strand = 1.09; 95% CI: 0.74–1.62; P = 0.67. Hazard ratio both aortic and mitral valvular strands = 0.81; 95% CI: 0.35–1.85; P = 0.61.

*Event rates are calculated from Kaplan-Meier curves at 2 years. Hazard ratios are calculated with no valvular strands as the reference group.

**TABLE 2C. Two-Year Rates of Recurrent Stroke or Death in Cryptogenic Patients With Valvular Strands Depending on Strand Location**

<table>
<thead>
<tr>
<th></th>
<th>No Strand (N=161)</th>
<th>Any Strand (N=101)</th>
<th>Only Aortic Strand (N=16)</th>
<th>Only Mitral Strand (N=71)</th>
<th>Both Aortic and Mitral Strands (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>11.9</td>
<td>15.0</td>
<td>12.5</td>
<td>17.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Events</td>
<td>13S/6D</td>
<td>11S/4D</td>
<td>2S/0D</td>
<td>8S/4D</td>
<td>1S/0D</td>
</tr>
</tbody>
</table>

Hazard ratio aortic valvular strand = 1.07; 95% CI: 0.25–4.60; P = 0.93. Hazard ratio mitral valvular strand = 1.52; 95% CI: 0.74–3.14; P = 0.25. Hazard ratio both aortic and mitral valvular strands = 0.59; 95% CI: 0.08–4.43; P = 0.61.

*Event rates are calculated from Kaplan-Meier curves at 2 years. Hazard ratios are calculated with no valvular strands as the reference group.

**TABLE 2D. Two-Year Rates of Recurrent Stroke, TIA, or Death in Cryptogenic Patients With Valvular Strands Depending on Strand Location**

<table>
<thead>
<tr>
<th></th>
<th>No Strand (N=161)</th>
<th>Any Strand (N=101)</th>
<th>Only Aortic Strand (N=16)</th>
<th>Only Mitral Strand (N=71)</th>
<th>Both Aortic and Mitral Strands (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>15.6</td>
<td>20.9</td>
<td>12.5</td>
<td>26.4</td>
<td>7.1</td>
</tr>
<tr>
<td>Events</td>
<td>11S/10T/5D</td>
<td>11S/6T/4D</td>
<td>2S/0T/0D</td>
<td>8S/6T/4D</td>
<td>1S/0T/0D</td>
</tr>
</tbody>
</table>

Hazard ratio aortic valvular strand = 0.78; 95% CI: 0.18–3.28; P = 0.73. Hazard ratio mitral valvular strand = 1.72; 95% CI: 0.94–3.14; P = 0.08. Hazard ratio both aortic and mitral valvular strands = 0.42; 95% CI: 0.06–3.11; P = 0.40.

*Event rates are calculated from Kaplan-Meier curves at 2 years. Hazard ratios are calculated with no valvular strands as the reference group.

**Discussion**

Several reports have demonstrated the association between valvular strands and stroke, particularly in younger patients.1–4 Valvular strands are thought to represent Lambl ex crescences, which are a filiform structure initially identified on aortic valve by Lambl and then by Magarey on the aortic valve.10–12 Typically, strands can only be detected in vivo by TE. They are thought to form because of “wear and tear” of the valve, associated with fibrin deposition over damaged endocardial valvular surfaces that subsequently become partially detached from the valve, condensed, hyalinized, and ultimately fibrosed. When these structures be-
come large, they are referred to as “giant Lambl excrescences” and are difficult to distinguish from papillary fibroelastoma. Valvular strands appear to remain intact without changes in appearance over a period of several years. Strands have also been described on prosthetic valves. However, they are thought to represent different material compared with those found on the native valves. As a mechanism for embolic events, it is possible that either the strands themselves break and embolize or the thrombi form on the strands that subsequently embolize. Indeed, thrombus on the strands has been previously described, prompting the use of warfarin. For this reason, some of the analyses included patients with strands on either the mitral or the aortic position considered together, rather than analyzing them separately. However, the exact mechanism through which strands are associated with stroke has not been established, and it is possible that there is no direct link between ischemic stroke and the presence of the strands.

The best treatment modality to prevent recurrent events in patients with strands has not been defined. There is only 1 previous study that assessed the recurrent event rates in patients with valvular strands. It suggested that the presence of strands did not increase the chance of adverse events but included only patients aged 60 or older with mitral strands, and medical therapy was not randomized. As such, the adverse event rate in stroke patients that included patients from different age groups or with strands on different valves has never been defined. Most importantly, the efficacy of

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**TABLE 3A. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without Valvular Strands Assigned to Warfarin or Aspirin**

<table>
<thead>
<tr>
<th>Strands (N=244)</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands events</td>
<td>13.5% (N=126)</td>
<td>19.6% (N=118)</td>
<td>0.67 (0.36–1.26)</td>
<td>0.21</td>
</tr>
<tr>
<td>No strands</td>
<td>16.5% (N=375)</td>
<td>14.6% (N=193)</td>
<td>2.12 (1.72–8.01)</td>
<td>0.48</td>
</tr>
<tr>
<td>No strand events</td>
<td>255/6D</td>
<td>185/10D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For Tables 3A–3D, S indicates stroke; T, transient ischemic attack; D, death. *From Kaplan-Meier curves.

**TABLE 3B. Two-Year Rates of Recurrent Stroke, TIA, or Death* in Patients With and Without Valvular Strands Assigned to Warfarin or Aspirin**

<table>
<thead>
<tr>
<th>Strands (N=244)</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands events</td>
<td>19.1% (N=126)</td>
<td>23.3% (N=118)</td>
<td>0.77 (0.45–1.33)</td>
<td>0.34</td>
</tr>
<tr>
<td>No strands</td>
<td>21.4% (N=375)</td>
<td>18.2% (N=193)</td>
<td>1.30 (0.83–2.03)</td>
<td>0.26</td>
</tr>
<tr>
<td>No strand events</td>
<td>245/12T/5D</td>
<td>155/10T/10D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From Kaplan-Meier curves.

**TABLE 3C. Two-Year Rates of Recurrent Stroke or Death* in Cryptogenic Patients With and Without Valvular Strands Assigned to Warfarin or Aspirin**

<table>
<thead>
<tr>
<th>Strands (N=101)</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands events</td>
<td>9.5% (N=42)</td>
<td>18.9% (N=59)</td>
<td>0.49 (0.16–1.53)</td>
<td>0.22</td>
</tr>
<tr>
<td>No strands</td>
<td>8.6% (N=161)</td>
<td>15.3% (N=79)</td>
<td>0.55 (0.22–1.41)</td>
<td>0.21</td>
</tr>
<tr>
<td>No strand events</td>
<td>55/2D</td>
<td>85/4D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From Kaplan-Meier curves.

**TABLE 3D. Two-Year Rates of Recurrent Stroke, TIA, or Death* in Cryptogenic Patients With and Without Valvular Strands Assigned to Warfarin or Aspirin**

<table>
<thead>
<tr>
<th>Strands (N=101)</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands events</td>
<td>14.3% (N=42)</td>
<td>25.7% (N=59)</td>
<td>0.51 (0.20–1.32)</td>
<td>0.17</td>
</tr>
<tr>
<td>No strands</td>
<td>12.2% (N=161)</td>
<td>19.2% (N=79)</td>
<td>0.71 (0.33–1.54)</td>
<td>0.38</td>
</tr>
<tr>
<td>No strand events</td>
<td>55/5T/1D</td>
<td>65/5T/4D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From Kaplan-Meier curves.
different medical regimens has never been addressed in a randomized fashion.

Our study found a mitral or aortic valve strand prevalence of 39.4% and mitral valve strand prevalence of 27.8% in the overall study population. This is similar to that described by Cohen of 22.5% on the mitral valve, by Roldan of 41% on any cardiac valve, and from our group previously of 47% in a separate series of patients. However, these prevalences are higher than those reported by Tice and Freedberg, possibly because of the difference in the characteristics of the patients or technical factors. In the current series, there was no difference in the prevalence between the cryptogenic and noncryptogenic patients. Similarity of valve strand prevalence in cryptogenic and noncryptogenic stroke patients has previously been reported and suggests that it may not be a risk factor for cryptogenic stroke.

The current study design did not address whether valvular strands are risk factors for initial stroke or the potential mechanism of stroke in patients with strands. We demonstrate that when the stroke patients are treated medically, the rate of recurrent stroke or death is similar between those with and without valvular strands. As such, surgical interventions are not indicated for the type of strands investigated in this study. Furthermore, when the efficacy of warfarin was compared with aspirin, there was no significant difference in the time to primary endpoints. However, because all patients were treated, it remains undefined whether the medical therapy altered the event rates if compared with untreated patients.

Our data are unique in that the patients were randomly, double-blindly assigned to warfarin or aspirin. This randomization process yielded similar numbers of patients assigned to warfarin and aspirin and, in those using warfarin, maintenance of target INR throughout the study period was confirmed. Furthermore, all TE studies were centrally, blindly analyzed using uniform criteria. Patients were then rigorously followed up for adverse events and each endpoint adjudicated by an expert panel blinded to treatment. We conclude that in medically treated stroke patients, the presence of valvular strands does not increase the chance of adverse events and that neither aspirin nor warfarin demonstrates an advantage with respect to treatment efficacy. Limitations of the study include relatively small numbers of patients in subgroups and the lack of control population. For strands, there was 80% power to detect a relative increase in risk of 80%, and for warfarin therapy, there was 80% power to detect a 67% decrease in risk of adverse events. Also, the analysis of the tapes was performed by a single experienced observer rather than by a panel of observers. Nevertheless, to our knowledge, this study remains the first randomized treatment study of stroke patients with valvular strands.

Appendix

Study Participants
National Institute of Neurological Disorders and Stroke (NINDS): J.R. Marler, Program Director


NINDS PSMB members: D.G. Sherman (Chair), M.L. Dyken, A. Lowe, L. Meissner, D.W. Taylor


Hemorrhage Adjudicator: A.G.G. Turpie

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References
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