Data Alert™

Expanding opportunities for secondary prevention of stroke

Dear Colleague:

Between 1979 and 2001, the number of patients discharged from the hospital with a primary diagnosis of stroke increased by 25%. Atrial fibrillation (AF) is a major cause of stroke, but anticoagulant therapy in patients with the arrhythmia greatly reduces the risk. Thus, detection of AF in stroke patients is essential. This Data Alert reviews recent studies on the implications of AF for in-hospital prognosis following acute stroke and discusses a possible algorithm to improve detection of the arrhythmia.

A number of studies have demonstrated that AF is associated with greater stroke severity. Most recently, Steger et al compared the in-hospital course of therapy following stroke or transient ischemic attack (TIA) in patients with and without AF. Their findings extend previous data by showing that, compared to patients without AF, stroke in patients with AF is associated with an increased rate of medical as well as neurological complications. At admission, patients with AF had a lower Barthel Index (15 vs 40) and a higher proportion had a Rankin Scale score of 5 (52% vs 31%), all of which, consistent with previous studies, indicated a more severe stroke.

<table>
<thead>
<tr>
<th>AF worsens prognosis following stroke</th>
<th>With AF</th>
<th>Without AF</th>
</tr>
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<tbody>
<tr>
<td>More severe stroke on admission</td>
<td></td>
<td></td>
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<tr>
<td>- Lower Barthel Index</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>- Higher proportion with Rankin Scale score (%)</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>Higher rate of medical complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pneumonia (%)</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>- Pulmonary edema (%)</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>- Symptomatic intracerebral hemorrhage (%)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>- Mortality (%)</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Poorer neurological status at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lower Barthel Index</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>- Higher Rankin Scale score</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

P < 0.0004 for all comparisons

Steger et al.

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Steger et al also showed that stroke/TIA patients with AF had a greater rate of in-hospital pneumonia (23% vs 9%), pulmonary edema (12% vs 6%), symptomatic intracerebral hemorrhage (8% vs 2%), and mortality (25% vs 14%). At discharge, patients with AF had a poorer neurological status, as measured by a lower Barthel Index (60 vs 85) and higher Rankin Scale score (4 vs 2). All comparisons between patients with and without AF were significant at P < 0.0004.

**New algorithm to improve detection of AF following stroke/TIA**

<table>
<thead>
<tr>
<th>Stroke/TIA</th>
<th>No. AF detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>Additional ECG</td>
<td>Yes 6 (4.1%)</td>
</tr>
<tr>
<td>24-hr Holter</td>
<td>Yes 7 (4.9%)</td>
</tr>
<tr>
<td>7-day ELR</td>
<td>Yes 5 (5.7%)</td>
</tr>
</tbody>
</table>

ELR = 2-lead event-loop recording device

Evaluation of stroke patients with a single standard electrocardiogram (ECG) will not identify all patients with AF, since this test has low sensitivity for the arrhythmia. That AF is frequently asymptomatic likely contributes to the underdiagnosis of AF in these patients. Jabaudon et al reported on a new algorithm that can help neurologists and cardiologists work together to diagnose AF in stroke patients. Patients were assessed in a stepwise manner via a standard 12-lead ECG (with 1–2 additional ECGs performed if clinical signs suggested an arrhythmia), followed by a 24-hour, 3-channel Holter recording, and, finally, 7-day monitoring using a 2-lead event-loop recording (ELR) device.

As shown, an initial ECG evaluation detected AF in 4 patients. Additional ECG evaluations within 5 days detected AF in an additional 6 patients. Holter monitoring (conducted at a median of 8 days after admission) detected AF in 7 of 139 patients with normal ECG. Finally, ELR monitoring (conducted at a median of 55 days after admission) detected AF in 5 of 88 evaluable patients with normal ECG and Holter recordings.
The graph of AF risk according to the length of monitoring showed that the risk of AF (calculated by Kaplan-Meier analysis) was approximately 6% after ECG monitoring and 16% after extended ELR monitoring.\(^4\)

The diagnostic algorithm used by Jabaudon et al. was not rigorous, with a relatively long delay (median of 55 days) before ELR monitoring, along with a relatively brief 7-day ELR-monitoring period. Nevertheless, these investigators demonstrated that, following stroke/TIA, cases of AF remain undetected by standard ECG or 24-hour Holter.\(^4\) These patients can be identified using an ELR device that permits longer duration of monitoring.

Similar recurrence rate regardless of method of detection

\(^{Jaboudon et al.}\)
A follow-up study performed 13 months later by Jabaudon et al showed that even after cardioversion and amiodarone treatment, AF recurred in 56% of patients who were diagnosed via ECG or 24-hour Holter and in 40% of those who were diagnosed via ELR. These findings, which are consistent with other studies, 1) show that AF tends to recur and, therefore, usually cannot be considered completely suppressed; 2) demonstrate that the natural history of episodic AF can be detected by ELR when other recording techniques fail; and 3) that chronic anticoagulation therapy is indicated in all AF patients following stroke or TIA regardless of how the arrhythmia is detected. Moreover, when the etiology of the stroke or TIA is not evident, a rigorous and aggressive search for AF should be pursued.

**Clinical implications**

- AF continues to present an enormous public health problem
  - Men and women >40 years have a lifetime risk for AF of ~1 in 4
  - Estimated 2.2 million Americans
  - May account for up to 140,000 strokes yearly
- ECG and 24-hr Holter monitoring do not identify all stroke/TIA patients with AF
- Many AF patients are not receiving anticoagulant therapy to prevent recurrent stroke

Data from the Framingham Heart Study (obtained before widespread use of modern antiarrhythmic therapies) suggest that men and women over the age of 40 years have a lifetime risk for AF of approximately 1 in 4. The arrhythmia currently affects an estimated 2.2 million people in this country and may account for up to 20% of all strokes, or 140,000 yearly. AF is likely to become an even greater contributor to the burden of stroke as the population ages. However, as the slides above demonstrate, improved detection of the arrhythmia in patients following stroke or TIA is needed.

**Towards optimal anticoagulant therapy in stroke prevention**

- AF should be strongly suspected in all patients with acute stroke/TIA or TIA
  - All stroke/TIA patients with confirmed AF should receive anticoagulant therapy
- Warfarin
  - Pro: Proven effective
  - Con: Need for frequent (and costly) monitoring and dose adjustment
- New anticoagulants that offer fixed dosing with no monitoring are under investigation and may address warfarin's shortcomings
  - Oral (direct thrombin inhibitors, ie, ximelagatran)
  - Parenteral (low–molecular-weight heparins, factor Xa inhibitors)

AHA, Jabaudon et al, Lloyd-Jones et al.
All stroke or TIA patients with AF should receive anticoagulant therapy. However, the benefits of warfarin (the only oral anticoagulant currently available) are offset by numerous drug and food interactions that greatly complicate the task of achieving and maintaining an INR within the therapeutic range. Thus, warfarin therapy requires frequent (and costly) monitoring and dose adjustment. Oral (direct thrombin inhibitors) and parenteral (low–molecular-weight heparins, factor Xa inhibitors) anticoagulants that offer fixed dosing with no monitoring are under investigation and may address warfarin’s shortcomings.

**SUMMARY AND CONCLUSIONS**

AF should be strongly suspected in all patients with acute stroke or TIA. Detection of AF can then help guide management by establishing a probable cause for the acute cerebral event. However, the data suggest a need to improve detection of this arrhythmia and to maintain an effective level of anticoagulation while minimizing risk of bleeding. A recently published stepwise diagnostic protocol is one possible option for addressing the first challenge (possibly utilizing a longer ECG-monitoring period of up to 30 days). As to the second, however, we must await results of ongoing studies of new anticoagulants.

Sincerely,

Carl J. Pepine, MD

**REFERENCES**