What Is Certain When the Stroke Etiology Is Uncertain?

Gustavo Saposnik, MD, MSc, FAHA, FRCPc

See related article, p 2948.

“Medicine is a science of uncertainty and an art of probability.”

—William Osler (1849–1919)

The great majority of ischemic strokes are due to cardioembolism, large-artery atherosclerotic disease, small-vessel occlusive disease, or other unusual mechanisms (eg, cervical dissection, thrombophilia, etc).1 Nevertheless, in approximately 20% to 40% of patients with stroke, the underlying etiology is not established (called “cryptogenic,” “uncertain,” or “undetermined” stroke).2 3 Limited information is available on long-term outcomes in this specific subgroup.

Clinicians wonder about the risk of recurrence and whether death and/or disability in patients with cryptogenic stroke are better or worse compared with those with a determined etiology.

In the present study, Nam et al studied 3278 patients with an ischemic stroke with a median follow-up of 3.4 years.4 Overall, 37% were classified as “undetermined.” Two thirds of patients had a mild stroke (National Institutes of Health Stroke Scale <6) with an overall median National Institutes of Health Stroke Scale of 4. Nearly 40% were exposed to smoking and 31% had diabetes. Interestingly, the authors broke down the undetermined strokes into 3 subgroups, including: multiple causes, negative evaluation, and incomplete evaluation. Criteria for incomplete evaluation included lack of “essential studies” (defined as parenchymal and vascular imaging, electrocardiographic or prothrombotic evaluation when appropriate). Of note, transthoracic echocardiogram was not considered “essential.” The prevalence of undetermined etiology stratified by age is summarized in the Table. The great majority of patients with undetermined stroke had negative investigations. A smaller percentage of patients had incomplete evaluation when stratified by age groups (<59 years: 4.1%, 60–79 years: 4.8% and >80 years: 7.1%). Poor functional outcome was defined at modified Rankin Scale from 3 to 6. Patients with undetermined stroke among those with incomplete evaluation during hospitalization had worse functional outcomes at 3 months (49.6% versus 24.5%; P<0.001). Similarly, this group had also the highest mortality at 30 days (12.5%), at 1 year (25.5%), and at 3 years (35.7%) compared with other stroke subtypes. These findings were confirmed in the adjusted analysis.

What Are the Limitations of This Study?

This is a single-center study with a potential for selection bias or misclassification. In other words, those patients classified as “undetermined etiology with incomplete investigations” may have been too sick to receive the required studies during the hospitalization. This is also true for those patients who died early after hospitalization. Approximately 50% of deaths occurred within the first 30 days; it is unclear if mortality was at 48 hours or at discharge. The authors adjusted for length of hospital stay to ameliorate this phenomenon. Finally, estimates in small sample sizes may not be accurate.

What Can We Learn From This Article?

Information reporting outcomes in patients with undetermined stroke is scarce and more so for those attempting to compare outcomes between patients with negative and incomplete investigations. Interestingly, only 20% of patients with stroke were classified as cardioembolic subtype. Furthermore, echocardiograms were not mandatory. Consequently, it is possible that poorer outcomes observed among patients with incomplete investigations could have had a cardiac source of embolism, usually associated with larger strokes and adverse outcomes.1

Considering the time pressures to discharge patients at the same time as providing comprehensive (and effective) stroke care, clinicians argue about the value of cardiac studies during the hospitalization. Some studies showed that a transthoracic echocardiogram has a low yield, and as such, guidelines do not formally recommend it as a mandatory study.1 5 Limited evidence is available because not many studies have satisfactorily addressed this issue. Echocardiography allows the diagnosis of atheroma in the aortic arc, vegetation (infective or nonbacterial origin), intra-cardiac tumors, and thrombus, among other high-risk cardiac sources of cerebral embolism. Transthoracic echocardiogram is easier, noninvasive, and widely available. The yield of a transthoracic echocardiogram in patients with stroke with clinically apparent heart disease is approximately 25%, whereas in patients without clinical heart disease, the yield is <10%.6 7

Where Do We Go From Here?
The diagnosis of the stroke mechanism could be difficult, especially in young individuals or when the initial (standard) evaluation is negative. Understanding risks and dealing with uncertainty in medicine are also challenging.
Three simple steps may guide clinicians: (1) rethink the stroke mechanism; (2) target ancillary investigations; and (3) follow-up.

Current guidelines do not recommend a routine transthoracic echocardiogram or transesophageal echocardiography in patients with an ischemic stroke. Limited evidence is available on this issue. The present study provides some evidence from the “back door.” When transthoracic echocardiogram is not routinely required, patients with stroke with undetermined stroke and incomplete investigations have worse short- and long-term outcomes.

Furthermore, identifying the underlying mechanism is crucial to select the appropriate treatment to prevent a recurrent vascular event. Can we establish the stroke mechanism without completing a cardiac evaluation? Can we classify patients with stroke as “cryptogenic” without at least completing an echocardiogram? Internists may argue about the limited evidence, whereas policymakers and administrators are concerned with decreasing the length of stay and reducing costs. However, we (neurologists trained in cerebrovascular disease) are the ones responsible to determine the stroke mechanism, suggest the necessary evaluation, and recommend the appropriate treatment.

Together, we should make the effort in completing the necessary investigations to determine the stroke mechanism, hopefully before patients are discharged.

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**Disclosures**

None.

**References**


**Key Words:** cerebrovascular disease • echocardiography • embolic stroke • ischemic stroke • prognosis • stroke care

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**Table. Baseline Characteristics According to Ischemic Stroke Subtype**

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Overall (n=3278)</th>
<th>≤59 y (n=1054)</th>
<th>60–79 y (n=1961)</th>
<th>≥80 y (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>811 (24.7)</td>
<td>209 (19.8)</td>
<td>541 (27.6)</td>
<td>61 (23.2)</td>
</tr>
<tr>
<td>CE</td>
<td>682 (20.8)</td>
<td>204 (19.3)</td>
<td>397 (20.2)</td>
<td>81 (30.8)</td>
</tr>
<tr>
<td>LAC</td>
<td>489 (14.9)</td>
<td>171 (16.2)</td>
<td>291 (14.8)</td>
<td>27 (10.2)</td>
</tr>
<tr>
<td>SOD</td>
<td>94 (2.9)</td>
<td>71 (6.7)</td>
<td>22 (1.1)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>UM</td>
<td>349 (10.6)</td>
<td>100 (9.5)</td>
<td>216 (11.0)</td>
<td>33 (12.5)</td>
</tr>
<tr>
<td>UN</td>
<td>696 (21.2)</td>
<td>256 (24.2)</td>
<td>399 (20.3)</td>
<td>41 (15.6)</td>
</tr>
<tr>
<td>UI</td>
<td>157 (4.8)</td>
<td>43 (4.1)</td>
<td>95 (4.8)</td>
<td>19 (7.2)</td>
</tr>
</tbody>
</table>

LAA indicates large-artery atherosclerosis; CE, cardioembolism; LAC, lacune; SOD, stroke of other determined etiology; UM, stroke of undetermined etiology due to multiple causes; UN, stroke of undetermined etiology due to negative evaluation; UI, stroke of undetermined etiology due to incomplete evaluation. Numbers between brackets represent percentages.

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