Cryptogenic Stroke and Occult Atrial Fibrillation

2015 Cardiac Dysrhythmia Conference

Bogachan Sahin, M.D., Ph.D.
Assistant Professor, Department of Neurology
Associate Director, Vascular Neurology Fellowship Program
University of Rochester School of Medicine and Dentistry

March 20th, 2015

DISCLOSURES
LECTURE OUTLINE

Stroke Basics

Case 1

Stroke Mechanisms

Cryptogenic Stroke

EMBRACE

CRYSTAL AF

Case 2

Outcomes

Conclusions

A Word about Prevention

LECTURE OUTLINE

Stroke Basics

Case 1

Stroke Mechanisms

Cryptogenic Stroke

EMBRACE

CRYSTAL AF

Case 2

Outcomes

Conclusions

A Word about Prevention
WHAT IS AN ACUTE ISCHEMIC STROKE?

Classic (clinical) definition:
- Sudden loss of focal neurologic function
- Attributable to ischemia
- Causing a focal neurologic deficit lasting 24 hours or more
- This definition does not capture all instances of CNS infarction.

Updated (tissue) definition:
- Brain, spinal cord, or retinal cell death
- Attributable to ischemia
- Based on evidence of permanent tissue injury
- This definition captures “silent” strokes, MRI-positive TIAs etc.
STROKE IN NUMBERS

- Fifth leading cause of death
- The leading cause of long-term disability in adults
- 800,000 strokes expected in 2015
- Nearly 1/4 recurrent
- Nearly 1/6 expected to die
- 90 strokes and 15 deaths in the U.S. per hour
- 7 strokes and 1 death in Rochester per day
- Up to 2/3 of survivors left with mild to severe disability
- 1/3 of stroke survivors suffer from depression
- Economic burden more than $30 billion per year

LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention
CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
- Mechanical embolectomy;
- No clinical improvement;
- Follow-up CT confirms massive left hemispheric infarct;
- Further work-up reveals “new-onset” atrial fibrillation.
CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
- Mechanical embolectomy;
- No clinical improvement;
- Follow-up CT confirms massive left hemispheric infarct;
- Further work-up reveals “new-onset” atrial fibrillation.
CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
  - Mechanical embolectomy;
  - No clinical improvement;
  - Follow-up CT confirms massive left hemispheric infarct;
  - Further work-up reveals “new-onset” atrial fibrillation.

CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
- Mechanical embolectomy;
- No clinical improvement;
- Follow-up CT confirms massive left hemispheric infarct;
- Further work-up reveals “new-onset” atrial fibrillation.
CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

• Presents with acute mutism and right-sided flaccid hemiplegia;
• Initial CT unrevealing;
• CTA shows a left MCA occlusion;
• Mechanical embolectomy;
• No clinical improvement;
  • Follow-up CT confirms massive left hemispheric infarct;
  • Further work-up reveals “new-onset” atrial fibrillation.
Case 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
- Mechanical embolectomy;
- No clinical improvement;
- Follow-up CT confirms massive left hemispheric infarct;
- Further work-up reveals “new-onset” atrial fibrillation.
CASE 1

Could we have prevented this outcome?

LECTURE OUTLINE

Stroke Basics
  Case 1
Stroke Mechanisms
  Cryptogenic Stroke
  EMBRACE
  CRYSTAL AF
  Case 2
Outcomes
Conclusions
A Word about Prevention
MECHANISMS OF ACUTE ISCHEMIC STROKE

Thrombotic

Lacunar

Embolic

Hemodynamic

Thrombotic:

- Large-vessel occlusive disease
  - Cervical and major intracranial vessels
  - Atherothrombosis
  - Dissection, vasculitis etc. less common
MECHANISMS OF ACUTE ISCHEMIC STROKE

Lacunar:

- Small-vessel occlusive disease
  - Deep penetrators
  - Lipohyalinosis
  - Atherothrombosis

Embolic:

- Heart
  - Atrial fibrillation
  - Endocarditis
  - Mechanical valve
  - Low ejection fraction
  - Left ventricular aneurysm
  - Mural thrombus
  - Patent foramen ovale etc.
- Aorta
  - Large ulcerated plaque
  - Mobile element
- Cervical and major intracranial arteries
- Thrombophilia
MECHANISMS OF ACUTE ISCHEMIC STROKE

Hemodynamic:

- Systemic or local hypoperfusion
- Classically affects the so-called "watershed" areas.

MECHANISMS OF ACUTE ISCHEMIC STROKE

- Atherothrombotic (25-30%)
- Cardioembolic (20%)
- Lacunar (15-20%)
- Cryptogenic (25-30%)
- Other (5-10%, e.g. hemodynamic)
MECHANISMS OF ACUTE ISCHEMIC STROKE

- Atherothrombotic (25-30%)
- Cardioembolic (20%)
- Lacunar (15-20%)
- Cryptogenic (25-30%)
- Other (5-10%, e.g. hemodynamic)
MECHANISMS OF ACUTE ISCHEMIC STROKE

• Atherothrombotic (25-30%)
• Cardioembolic (20%)
• Lacunar (15-20%)
• Cryptogenic (25-30%)
• Other (5-10%, e.g. hemodynamic)
LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention

SOME DEFINITIONS

• Cryptogenic stroke
  Ischemic stroke of unknown cause

• Occult atrial fibrillation
  Unrecognized paroxysmal AF
  It may require prolonged monitoring for detection.
CRYPTOGENIC STROKE

- 25-30% strokes remain idiopathic after a thorough investigation.
- Some of these patients may have occult AF.
- They are typically treated with antiplatelet agents.
- Detection of AF has the potential to change management.
- Change in management has the potential to improve outcomes.

LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention
EMBRACE

- Investigator-initiated, open-label, multicenter RCT (Canada)
- Funding source: Academic
- 572 cryptogenic stroke or TIA patients ≥ 55 years
- Randomized to 30-day auto-trigger external cardiac event monitor vs. 24-hour Holter monitor
- Primary outcome: AF lasting ≥ 30 seconds within 90 days
- Secondary outcomes:
  - AF lasting ≥ 30 seconds and ≥ 150 seconds
  - AF of any duration
  - Anticoagulation status at 90 days
EMBRACE

• Primary outcome:
  16.1% (intervention) vs. 3.2 % (control) of patients

• Secondary outcomes:
  AF ≥ 30 sec detected in 15.5% (intervention) vs. 2.5 % (control)
  AF ≥ 150 sec detected in 9.9% (intervention) vs. 2.5 % (control)
  Any AF detected in 19.7% (intervention) vs. 4.7 % (control)
EMBRACE

- Secondary outcomes:
  Anticoagulation status at 90 days
  OAC in 18.6% (intervention) vs. 11.6% (control) of patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Intervention Group (N=280)</th>
<th>Control Group (N=280)</th>
<th>Difference (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant therapy before index stroke</td>
<td>77 (27.5) (14.6)</td>
<td>21 (7.5) (5.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anticoagulant therapy at randomization after index stroke or TIA</td>
<td>16 (5.7) (5.4)</td>
<td>16 (5.7) (6.7)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

After study enrolling

<table>
<thead>
<tr>
<th>Therapy at 30 days after randomization</th>
<th>Intervention Group (N=280)</th>
<th>Control Group (N=280)</th>
<th>Difference (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant therapy</td>
<td>221 (79.3) (79.6)</td>
<td>246 (88.2) (88.2)</td>
<td>-8.9 (1.6 to -12.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anticoagulant therapy only</td>
<td>221 (79.3) (79.6)</td>
<td>246 (88.2) (88.2)</td>
<td>-8.9 (1.6 to -12.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Therapy at randomization changed by 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From anticoagulant therapy to anticoagulant therapy</td>
<td>18 (6.4) (13.8)</td>
<td>13 (4.6) (13.6)</td>
<td>8.9 (1.6 to 13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>From anticoagulant therapy to aspirin therapy</td>
<td>7 (2.5) (1.1)</td>
<td>2 (0.7) (0.7)</td>
<td>6.4 (1.2 to 13.4)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

EMBRACE

- Duration of monitoring improves diagnostic yield.
CRYSTAL AF

• Industry-sponsored multicenter RCT (N. America and Europe)
• 441 cryptogenic stroke or TIA patients ≥ 40 years
• Randomized to implantable cardiac monitor (ICM) vs. “standard therapy”
• Primary outcome: AF lasting ≥ 30 seconds within 6 months
• Secondary outcomes:
  - AF lasting ≥ 30 seconds within 12 months
  - Recurrent stroke or TIA
  - Initiation of oral anticoagulants
CRYSTAL AF

• Primary and secondary outcomes:

- CRYSTAL AF

- Parameter 6 Months 12 Months 36 Months
- Time to AF detection 41 days 84 days 252 days
- Asymptomatic episodes 74% 79% 81%
- Anticoagulant use among patients found to have AF 94.7% 96.6% 90.0%
- Patients with > 6 min of AF on 1 day 93.8% 92.3% 94.9%
EMBRACE vs. CRYSTAL AF

- The external event monitor detected AF in 16.1% of patients at 90 days in EMBRACE.
- The implantable event monitor detected AF in 8.9% of patients at 180 days in CRYSTAL AF.
- There were differences in initial stroke work-up.
  - TEE or intracranial imaging not required in EMBRACE
  - Less pre-enrollment ECG monitoring in EMBRACE
- There were differences in the control arms.
  - “ECG monitoring performed at the discretion of the site investigator” in the control arm CRYSTAL AF
- Average age 73 vs. 61 in EMBRACE vs. CRYSTAL AF
EMBRACE vs. CRYSTAL AF

- The external event monitor detected AF in 16.1% of patients at 90 days in EMBRACE.
- The implantable event monitor detected AF in 8.9% of patients at 180 days in CRYSTAL AF.
- There were differences in initial stroke work-up.
  - TEE or intracranial imaging not required in EMBRACE
  - Less pre-enrollment ECG monitoring in EMBRACE
- There were differences in the control arms.
  - “ECG monitoring performed at the discretion of the site investigator” in the control arm CRYSTAL AF
- Average age 73 vs. 61 in EMBRACE vs. CRYSTAL AF
EMBRACE vs. CRYSTAL AF

- The external event monitor detected AF in 16.1% of patients at 90 days in EMBRACE.
- The implantable event monitor detected AF in 8.9% of patients at 180 days in CRYSTAL AF.
- There were differences in initial stroke work-up.
  - TEE or intracranial imaging not required in EMBRACE
  - Less pre-enrollment ECG monitoring in EMBRACE
- There were differences in the control arms.
  - “ECG monitoring performed at the discretion of the site investigator” in the control arm CRYSTAL AF
- Average age 73 vs. 61 in EMBRACE vs. CRYSTAL AF

Selection criteria for implantable loop recorder placement in hospitalized patients with cryptogenic stroke

Patient Selection:

1. Age ≥ 40
2. Brain imaging consistent with cardioembolic stroke
3. No identifiable thromboembolic source after a thorough work-up
4. No history of atrial fibrillation or atrial flutter
5. No indication or contraindication for lifelong anticoagulation

Diagnostic Approach:

Patients ≥ 40 and < 55 should be offered an implantable loop recorder.
Patients ≥ 55 may be offered a 30-day cardiac event monitor or an implantable loop recorder, with the understanding that if the 30-day cardiac event monitor is unrevealing, an implantable loop recorder would be the next recommended step.
Selection criteria for implantable loop recorder placement in hospitalized patients with cryptogenic stroke

Patient Selection:

1. Age $\geq 40$
2. Brain imaging consistent with cardioembolic stroke
3. No identifiable thromboembolic source after a thorough work-up
4. No history of atrial fibrillation or atrial flutter
5. No indication or contraindication for lifelong anticoagulation

Diagnostic Approach:

Patients $\geq 40$ and $< 55$ should be offered an implantable loop recorder. Patients $\geq 55$ may be offered a 30-day cardiac event monitor or an implantable loop recorder, with the understanding that if the 30-day cardiac event monitor is unrevealing, an implantable loop recorder would be the next recommended step.

LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention
CASE 2

71-year-old woman with no known past medical history:

- Presented with transient slurred speech;
- CT showed old embolic infarcts;
- CTA showed no significant atherosclerotic disease;
- MRI showed acute multifocal embolic left MCA infarcts;
- TTE: Left atrial enlargement;
- TEE: Biatrial enlargement, no LAA thrombus;
- Discharged on ASA and statin therapy;
- Referred to Cardiology for implantable loop recorder placement;
- Paroxysmal AF detected, patient started on apixaban.
CASE 2

71-year-old woman with no known past medical history:

- Presented with transient slurred speech;
- CT showed old embolic infarcts;
- CTA showed no significant atherosclerotic disease;
- MRI showed multifocal embolic left MCA infarcts;
- TTE: Left atrial enlargement;
- TEE: Bialtrial enlargement, no LAA thrombus;
- Discharged on ASA and statin therapy;
- Referred to Cardiology for implantable loop recorder placement;
- Paroxysmal AF detected, patient started on apixaban.
CASE 2

71-year-old woman with no known past medical history:

- Presented with transient slurred speech;
- CT showed old embolic infarcts;
- CTA showed no significant atherosclerotic disease;
- MRI showed multifocal embolic left MCA infarcts;
- TTE: Left atrial enlargement;
- TEE: Biatrial enlargement, no LAA thrombus;
- Discharged on ASA and statin therapy;
- Referred to Cardiology for implantable loop recorder placement;
- Paroxysmal AF detected, patient started on apixaban.

LECTURE OUTLINE

Stroke Basics
  Case 1
Stroke Mechanisms
Cryptogenic Stroke
  EMBRACE
CRYSTAL AF
  Case 2
Outcomes
Conclusions
A Word about Prevention
LECTURE OUTLINE

Stroke Basics
  Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
  Case 2
Outcomes
Conclusions

A Word about Prevention
CONCLUSIONS

- Continuous monitoring increases diagnostic yield.
- AF detection changes management in most cases.
- It is unclear if this improves patient outcomes.

LECTURE OUTLINE

Stroke Basics
  Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
  Case 2
Outcomes
Conclusions
A Word about Prevention
CONTINUUM OF STROKE THERAPY

• Primary prevention
• Acute therapies (recanalization, neuroprotection etc.)
• Prevention of immediate complications
• Recovery and rehabilitation
• Secondary prevention
CONTINUUM OF STROKE THERAPY

- Primary prevention
- Acute therapies (recanalization, neuroprotection etc.)
- Prevention of immediate complications
- Recovery and rehabilitation
- Secondary prevention

No proven acute treatments beyond the first few hours
Intravenous rt-PA still the gold standard of acute care
Only 10% of ischemic stroke patients eligible
Not all eligible patients treated (e.g. 77% in 2011)
Only 12% of treated patients expected to benefit
That is fewer than 1% (about 0.8%) of all ischemic strokes.
CONTINUUM OF STROKE THERAPY

- Reducing blood pressure reduces stroke risk by 35 to 40%.
- Exercise can reduce stroke risk by 40%.
- Statins reduce stroke risk even in people with mildly elevated LDL.
- Smoking doubles the risk of stroke.
- Risk of stroke is 2 to 6 times higher in diabetics.

CONTINUUM OF STROKE THERAPY

- Nearly 800,000 strokes are expected in U.S. in 2015.
- About 680,000 of these will be ischemic strokes.
- Up to 200,000 will have no clear source.
- Up to 60,000 may be due to paroxysmal AF.
- Annual risk of recurrent stroke at least 4% in this group (2,400).
- Antiplatelets may reduce that risk to 3% (1,800).
- Anticoagulants expected to reduce it to 1.3% (800).
- At least 1,000 fewer strokes per year going forward.
- 1,500 assuming one other risk factor on average.
- 2,200 assuming two other risk factors on average.