Heart and Brain

Paolo Bovi
Stroke Unit – UO Neurologia A – DAI di Neuroscienze
Azienda Ospedaliera Universitaria Integrata Verona
I do not say so, but at least so...
Cardioembolic stroke
Diagnosis of CE stroke

- Clinical features
- Neuroimaging
- Biomarkers
- Evidence of CE source

CE Stroke
1) Clinical features

- **Sudden onset** with rapid achievement of complete deficit in a few minutes

- Possible alteration in **level of consciousness**

- Possible **spectacular and rapid regression** of symptoms in the case of fragmentation of the embolus and subsequent distal migration or complete recanalization

- **Aphasia** isolated

- **Other clinical situations** (headache, seizures at the beginning or onset of the deficit during exercise) are not really specific to the CE strokes although suggestive
Clinical Characteristics of CE TIA: comparison with non-CE TIA

Takeshi Hayashi et al.

Journal of Stroke & Cerebrovascular Diseases
Volume 23, Issue 8, Pages 2169-2173, September 2014

- Clinical and neuroimaging features are similar in TIA of CE and non-CE etiologies

- The CHADS2 score can be useful in assessing the probability of CE TIA
2) Neuroimaging

Infarct Pattern and Clinical Outcome in Acute Ischemic Stroke Following Middle Cerebral Artery Occlusion

Keon-Joo Lee, Keun-Hwa Jung, Jung-Ick Byun, Jeong-Min Kim, Jae-Kyu Roh

"Thrombotic and embolic occlusion mechanisms have different infarct patterns…"
One hundred and eighty patients with non-rheumatic atrial fibrillation and contraindication to warfarin therapy were enrolled in the PLAATO study. Patients were eligible if they had a history of transient ischaemic attack (TIA) or stroke or at least two independent risk factors for stroke such as age \( \geq 75 \) years, hypertension, congestive heart failure or diabetes. The primary endpoint was LAA closure as determined by transesophageal echocardiography (TEE) two months after the procedure and stroke rate at 150 patient years.

### 3) Biomarkers

**CE stroke diagnosis using Blood Biomarkers**

V. Llombart, J. Montaner et al.

*Current Cardiology Reviews, 2013, 9, 340-352*
Predicting CE stroke
with the B-Type Natriuretic Peptide Test: a Systematic Review and Meta-analysis.

Yanq HL et al.
J Stroke Cerebrovasc Dis 2014 May 1

“BNP has reasonable accuracy in the diagnosis of CE stroke...

May be a useful marker for the early detection in patients who may benefit from preventive OAC”.
4) Cardioembolic sources

“From the heart to the brain”: mechanisms of embolism

1) **Blood stasis and thrombus formation** in an enlarged (or affected by another structure alteration) left cardiac chamber (left atrial auricola, left ventricular aneurysm…)

2) **Release of material** from an abnormal valvular surface (e.g. calcific degeneration)

3) **Abnormal passage** from the venous to the arterial circulation (paradoxical embolism)

Ferro JM. Brain embolism: answers to practical questions. J Neurol 2003
Recent MI
Left ventricular thrombosis
Valvulopathy
Prosthetic valves
Other causes (PFO, DIA, atrial myxoma, aortic arch, etc.)
Incidence of stroke, in AF patients, increases with age

Incidence of stroke after diagnosis of AF (men)

22-year follow-up of 75,126 men in the Danish National Registry of Patients

Christian Doppler (1803-1853)

Poststroke atrial fibrillation: Cause or consequence?
Critical review of current views

L.A. Sposato, P.M. Riccio, V. Hachinski

“To which extent poststroke AF is the cause or the consequence of the stroke remains uncertain.”
1. Definitely a potential cause of the index stroke

(a) Mitral stenosis;
(b) Prosthetic heart valve;
(c) Myocardial infarction within the past 4 weeks;
(d) Mural thrombus in left cavities;
(e) Left ventricular aneurysm;
(f) Any documented history or permanent or transient AF or flutter with or without spontaneous echo contrast or left atrial thrombus;
(g) Sick sinus syndrome;
(h) Dilated cardiomyopathy;
(i) Ejection fraction <35%;
(j) Endocarditis;
(k) Intracardiac mass;
(l) PFO plus in situ thrombosis;
(m) PFO plus concomitant PE or DVT preceding the brain infarction.

2. Causality uncertain of the index stroke

(a) PFO and ASA;
(b) PFO and concomitant DVT or PE (but not preceding the IS);
(c) Spontaneous echo contrast;
(d) Apical akinesia of the left ventricle and impaired ejection fraction (>35%);
(e) Only suggested by history of MI or palpitation and multiple repeated brain infarcts on both sides or in both the anterior and posterior circulation;
(f) Only suggested by abdominal CT/MRI or autopsy demonstration of the presence of systemic infarction or lower limb embolism.

3. Unlikely a direct cause of index stroke

One of the following abnormalities: PFO, ASA, valvular strands, mitral annulus calcification, calcified aortic valve, nonapical akinesia of the left ventricle.
Relevant aspects of CE stroke

The most frequent
The most serious
The more tractable
The most recurrent
The bloodiest
The most preventable
### Acute Cardioembolic Cerebral Infarction: answers to clinical questions

Adrià Arboix and Josefina Alióc

*Current Cardiology Reviews 2012, 8, 54-67*

---

**Table 1. Distribution of Cerebral Infarctions According to Age in the Sagrat Cor Hospital of Barcelona Stroke Registry**

<table>
<thead>
<tr>
<th>Subtype of cerebral infarction (n = 1840)</th>
<th>&lt;65 (n=314)</th>
<th>65–74 (n=501)</th>
<th>75–84 (n=722)</th>
<th>≥ 85 (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic</td>
<td>46 (14.6)</td>
<td>100 (20)</td>
<td>213 (29.5)</td>
<td>109 (36)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>66 (21.0)</td>
<td>159 (31.7)</td>
<td>233 (32.3)</td>
<td>95 (31.4)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>93 (29.6)</td>
<td>159 (31.7)</td>
<td>173 (24)</td>
<td>59 (19.5)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>61 (19.4)</td>
<td>69 (13.8)</td>
<td>81 (11.2)</td>
<td>37 (12.2)</td>
</tr>
<tr>
<td>Unusual cause</td>
<td>48 (15.3)</td>
<td>14 (2.8)</td>
<td>22 (3.0)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>
There was a significant decline in LA and SA.

The proportion of CA increased from 26% in 2002 to 56% in 2012.

Our findings suggest more intensive investigation for CE sources and greater use of OAC.
Embolic strokes of undetermined source: 
the case for a new clinical construct

RG Hart for the Cryptogenic Stroke/ESUS International Working Group
The Lancet Neurology, Volume 13, Issue 4, Pages 429 - 438, April 2014
The most serious

- Hyperdense MCA
- “T” occlusion of carotid
- Basilar “top”

JS Mayer et al. Cerebral Embolization
Stroke 1971;2:541-554
The more tractable

Differential Pattern of Tissue Plasminogen Activator–Induced Proximal Middle Cerebral Artery Recanalization Among Stroke Subtypes

Carlos A. Molina, MD, PhD; Joan Montaner, MD, PhD; Juan F. Arenillas, MD; Marc Ribo, MD; Marta Rubiera, MD; José Alvarez-Sabín, MD, PhD

*(Stroke. 2004;35:486-490.)*

“Response to tPA may vary, depending on the size, composition, and source of the clot…

The pattern of tPA-induced MCA recanalization differs among stroke subtypes…

Early recanalization was more frequent, faster and more complete in patients with CE stroke”. 
The Impact of Histological Clot Composition in Embolic Stroke.
Boeckh-Behrens T. et al.
Clin Neuroradiol 2014 Sep 27.

Higher percentage of WBCs in the thrombus was associated with:
- cardioembolic etiology
- extended mechanical recanalization time
- less favorable recanalization and clinical outcome

Our results suggest that thrombi with a high WBC fraction are related to more organized thrombi of cardioembolic origin
The most recurrent

**Immediate Anticoagulation of Embolic Stroke: A Randomized Trial**

CEREBRAL EMBOLISM STUDY GROUP

*Stroke; Vol 14, No 5, 1983*

**Table 7 Risk of Early Recurrent Embolism after Embolic Stroke**

<table>
<thead>
<tr>
<th>Author</th>
<th>Cardiac source</th>
<th>N</th>
<th>Interval</th>
<th>Recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain &amp; systemic recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daly et al. (1951)</td>
<td>RHD</td>
<td>194</td>
<td>7 days</td>
<td>17%</td>
</tr>
<tr>
<td>Szekely (1964)</td>
<td>RHD</td>
<td>72</td>
<td>28 days</td>
<td>10%</td>
</tr>
<tr>
<td>Darling et al. (1967)</td>
<td>RHD</td>
<td>89</td>
<td>14 days</td>
<td>19%</td>
</tr>
<tr>
<td>Darling et al. (1967)</td>
<td>MI</td>
<td>28</td>
<td>14 days</td>
<td>18%</td>
</tr>
<tr>
<td>Darling et al. (1967)</td>
<td>AF</td>
<td>59</td>
<td>14 days</td>
<td>20%</td>
</tr>
<tr>
<td>Hart et al. (1983)</td>
<td>AF</td>
<td>23</td>
<td>14 days</td>
<td>13%</td>
</tr>
<tr>
<td>Fisher (1979)</td>
<td>AF/RHD</td>
<td>100</td>
<td>10 days</td>
<td>5%</td>
</tr>
<tr>
<td>Brain recurrence only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CESG (1983)</td>
<td>mixed</td>
<td>20</td>
<td>14 days</td>
<td>10%</td>
</tr>
<tr>
<td>Furlan et al. (1982)</td>
<td>mixed</td>
<td>23</td>
<td>7 days</td>
<td>22%</td>
</tr>
<tr>
<td>Koller (1982)</td>
<td>mixed</td>
<td>29</td>
<td>14 days</td>
<td>14%</td>
</tr>
<tr>
<td>Sage &amp; VanUitert (1983)</td>
<td>AF</td>
<td>59</td>
<td>14 days</td>
<td>2%</td>
</tr>
<tr>
<td>Bass (1982)</td>
<td>mixed</td>
<td>30</td>
<td>30 days</td>
<td>10%</td>
</tr>
<tr>
<td>Aggregate estimate†</td>
<td>mixed</td>
<td></td>
<td>14 days</td>
<td>11%</td>
</tr>
<tr>
<td>early recurrence to brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>14 days</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHD</td>
<td>14 days</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>14 days</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The **early** (within 14 days) recurrent rate of **mixed cardio-embolism** is **11%**.
"The risk of early recurrence appears to be spread evenly over the initial 14 days, with no "grace period" following stroke…"
Recurrent stroke in patients with and without atrial fibrillation
Plasma BNP as a Predictive Marker of Early Recurrent Stroke in CE stroke

Shibazaki et al.
J Stroke and Cerebr Dis 2014

- On multivariate analysis, plasma BNP ≥255 pg/mL was independently associated with recurrent stroke.
- Plasma BNP could be a useful marker for predicting early recurrent stroke during hospitalization in CE stroke patients.
“In this single center series, the incidence of early recurrent AIS after iv r-tPA was 2.6% and was associated with previous AF.”
“Hemorrhagic transformation is a regular finding in medium-sized and large (>10 cm³) CE infarcts… Thus, the severity and not the frequency, of hemorrhages into brain infarcts should be the matter of interest”.

Christian Doppler (1803-1853)
“Delayed recanalization, occurring >6 h after CE stroke, is an independent predictor of HT”.

Christian Doppler (1803-1853)
**HI-1**
Small petechiae along the margins of the infarct

**HI-2**
More confluent petechiae within the infarcted area, but without space-occupying effect

**PH-1**
Hematoma in <30% of the infarcted area with some slight space-occupying effect

**PH-2**
Dense hematoma >30% of the infarcted area, with substantial space-occupying effect
Early Hemorrhagic Transformation of Brain Infarction: Rate, Predictive Factors, and Influence on Clinical Outcome

Results of a Prospective Multicenter Study

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total (n=1125)</th>
<th>Without HT (n=1027)</th>
<th>With HI (n=62)</th>
<th>Significance</th>
<th>With PH (n=36)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>191 (17.0%)</td>
<td>170 (16.5%)</td>
<td>15 (24.2%)</td>
<td>0.12</td>
<td>6 (16.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>323 (28.7%)</td>
<td>315 (30.7%)</td>
<td>7 (11.3%)</td>
<td>0.001</td>
<td>1 (2.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>300 (26.7%)</td>
<td>249 (24.2%)</td>
<td>30 (48.4%)</td>
<td>0.0001</td>
<td>21 (58.3%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>213 (18.9%)</td>
<td>201 (19.6%)</td>
<td>8 (12.3%)</td>
<td>0.24</td>
<td>4 (11.1%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Other cause</td>
<td>54 (4.8%)</td>
<td>48 (4.7%)</td>
<td>2 (3.2%)</td>
<td>1.00</td>
<td>4 (11.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multiple causes</td>
<td>44 (3.9%)</td>
<td>44 (4.3%)</td>
<td>0</td>
<td>0.17</td>
<td>0</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Christian Doppler (1803-1853)
Paciano et al. Stroke 2008
<table>
<thead>
<tr>
<th>Immediate Anticoagulation for AIS in AF</th>
<th>Yes</th>
<th>Angel Chamorro</th>
<th>Stroke. 2006;37:3052-3053</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Anticoagulation for AIS in AF</td>
<td>No</td>
<td>Peter Sandercock</td>
<td>Stroke. 2006;37:3054-3055</td>
</tr>
<tr>
<td>Immediate Anticoagulation for AIS in AF</td>
<td>No, but . . .</td>
<td>Stephen M. Davis and Geoffrey A. Donnan</td>
<td>Stroke. 2006;37:3056</td>
</tr>
</tbody>
</table>
Our findings indicate that in patients with acute CE stroke, **early (<48 h) anticoagulation** (UFH, LMWH, heparinoid), is associated with:

- **a non-significant reduction** in recurrence of AIS
- **an increased** intracranial bleeding
Patients with ischaemic stroke of CE origin:

1) Bridging with heparins *is not required*

2) ASA has **no place** in secondary stroke prevention
Re-institution of anticoagulation:

1) **after 1 day:** TIA
2) **after 3 days:** small or non-disabling infarct
3) **after 6 days:** moderate stroke
4) **not before 2 or 3 weeks:** large infarcts involving large parts of the arterial territory
Can early effective anticoagulation prevent new lesions on MRI in acute CE stroke?

E. Nomura et al.

Journal of Stroke & Cerebrovascular Diseases
Volume 23, Issue 8, Pages 2099-2104, September 2014

“Our findings suggest that achieving targeted PT-INR at 2 weeks by using warfarin prevents new lesions in AIS patients with AF”.

Christian Doppler (1803-1853)
“In patients with recent CE stroke, what is the optimal time to start (or re-start) anticoagulation with a NOAC (or warfarin)?

**The optimal time is uncertain!**

“There are no clinical trial data evaluating the safety and efficacy of the NOACs in the first 7-14 days after ischaemic CE stroke”.

Christian Doppler (1803-1853)
No influence of Dabigatran anticoagulation on Hemorrhagic Transformation in an experimental model of ischemic stroke

W Pfeilschifter et al.

“The data suggest that DE does not significantly increase HT after focal cerebral ischemia in mice…

From a translational viewpoint, this indicates that a continuation of DE anticoagulation in case of an ischemic stroke might be safe; but clearly, clinical data on this question are warranted”.  

Christian Doppler (1803-1853)
“Rivaroxaban, in contrast to warfarin, does not increase secondary hemorrhage after IVT in experimental cerebral ischemia…

Less effects of rivaroxaban on post-ischemic BBB permeability may account for this difference”.
One hundred and eighty patients with non-rheumatic atrial fibrillation and contraindication to warfarin therapy were enrolled in the PLAATO study. Patients were eligible if they had a history of transient ischaemic attack (TIA) or stroke or at least two independent risk factors for stroke such as age $\geq$ 75 years, hypertension, congestive heart failure or diabetes. The primary endpoint was LAA closure as determined by transesophageal echocardiography (TEE) two months after the procedure and stroke rate at 150 patient years. Left atrial...
“It's very, very difficult to reconcile the heart and brain...
Do you think, in my case, you do not even talk”.

Woody Allen