Cardioembolic infarction accounts for approximately a quarter of all cerebral infarcts [1]. The macroscopic appearance of cardioembolic infarction in brain sections is shown in Figure 1. Cardioembolic stroke is the most severe ischemic stroke subtype, with a high in-hospital mortality rate (6–27%) and a substantial number of patients with neurological dysfunction at the time of hospital discharge; however, the risk of early embolic recurrence varies between 1 and 10% [1–8]. Some clinical aspects of the natural course of the disease are still poorly defined.

Embolism from the heart to the brain results from one of the following mechanisms: structural heart abnormalities (e.g., left ventricular aneurysm), cardiac valvular disease, right-to-left shunts (paradoxical embolism) and rhythm disturbance [2]. Cardiac emboli can be of any size, but those arising from the cardiac chambers are often large and therefore especially likely to cause severe stroke, disability and death.

The most relevant aspects of cardioembolic infarction discussed here included the following pathophysiology: clinical features; diagnostic testing; cardiac sources of embolism; outcome; blood biomarkers; special clinical conditions; and treatment (thrombolysis and anticoagulation).

Pathophysiology

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischemic stroke subtypes [9], a cardioembolic source is found in 21–37% of cases, atherothrombotic stroke accounts for 15–48% (much less than in coronary heart disease), small-vessel disease in 10–34% of cases and the etiology remains undetermined in as many as 30–38% of cases. Coronary heart disease and atherothrombotic cerebrovascular disease share similar pathological mechanisms and, consequently, many risk factors. The incidence of these risk factors, however, is different. For example, hypertension is the most frequent risk factor in both coronary heart disease and ischemic stroke, but diabetes, hyperlipidemia and obesity are more frequent in coronary heart disease, whereas atrial fibrillation and other sources of embolism are more common in ischemic stroke [10]. In addition, the incidence of risk factors also differs among the various stroke subtypes. Atrial fibrillation (75% of cases) and hypertension (49% of cases) predominate in patients with cardioembolic stroke (Table 1). In very elderly patients, cardioembolic infarcts are the most common stroke subtype (40% of cases), followed by atherothrombotic stroke and lacunar infarctions. Recent studies of atrial fibrillation have identified mutations in a series of ion channels [11]. Although these mutations appear to be relatively rare, a greater understanding of the genetics of atrial fibrillation should yield insights into novel pathways, therapeutic targets and diagnostic testing for this common arrhythmia.
Review
Arboix & Alió

Table 1. Cardiovascular risk factors in 2704 patients with cerebral infarction according to stroke subtype in the Sagrat Cor Hospital of Barcelona Stroke Registry.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total, n (%)</th>
<th>Atherothrombotic, n = 770 (%)</th>
<th>Lacunar, n = 733 (%)</th>
<th>Cardioembolic, n = 763 (%)</th>
<th>Undetermined etiology, n = 324 (%)</th>
<th>Unusual cause, n = 114 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1501 (55.5)</td>
<td>509 (66.1)*</td>
<td>525 (71.6)*</td>
<td>377 (49.4)*</td>
<td>59 (18.2)*</td>
<td>31 (27.2)*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>807 (29.8)</td>
<td>120 (15.6)*</td>
<td>81 (11.1)*</td>
<td>573 (75.1)*</td>
<td>25 (7.7)*</td>
<td>8 (7)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>632 (23.4)</td>
<td>242 (31.4)*</td>
<td>218 (29.7)*</td>
<td>142 (18.6)**</td>
<td>24 (7.4)*</td>
<td>6 (5.3)*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>480 (17.8)</td>
<td>164 (21.3)*</td>
<td>166 (22.6)*</td>
<td>88 (11.5)*</td>
<td>52 (16)*</td>
<td>10 (8.8)</td>
</tr>
<tr>
<td>Previous cerebral infarction</td>
<td>468 (17.3)</td>
<td>164 (21.3)**</td>
<td>117 (16)</td>
<td>146 (19.1)</td>
<td>31 (9.6)*</td>
<td>10 (8.8)**</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>435 (16.1)</td>
<td>150 (19.5)**</td>
<td>104 (14.2)</td>
<td>163 (21.4)*</td>
<td>14 (4.3)*</td>
<td>4 (3.5)*</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>317 (11.7)</td>
<td>116 (15.1)**</td>
<td>80 (10.9)</td>
<td>73 (9.6)**</td>
<td>37 (11.4)</td>
<td>11 (9.6)</td>
</tr>
<tr>
<td>Smoking (&gt;20 cigarettes/day)</td>
<td>260 (9.6)</td>
<td>87 (11.3)**</td>
<td>86 (11.7)*</td>
<td>28 (3.7)*</td>
<td>41 (12.7)*</td>
<td>18 (6.9)</td>
</tr>
<tr>
<td>COPD</td>
<td>223 (8.2)</td>
<td>74 (9.6)</td>
<td>61 (8.3)</td>
<td>62 (8.1)</td>
<td>20 (6.2)</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>214 (7.9)</td>
<td>100 (13)**</td>
<td>57 (7.8)</td>
<td>50 (6.6)</td>
<td>3 (0.9)**</td>
<td>4 (3.5)**</td>
</tr>
<tr>
<td>Valve heart disease</td>
<td>174 (6.4)</td>
<td>11 (1.4)*</td>
<td>21 (2.9)*</td>
<td>130 (17)*</td>
<td>6 (1.9)**</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 8 (5.5)</td>
<td>43 (5.6)</td>
<td>24 (3.3)**</td>
<td>72 (9.4)*</td>
<td>8 (2.5)**</td>
<td>1 (0.9)**</td>
</tr>
<tr>
<td>Obesity</td>
<td>118 (4.4)</td>
<td>36 (4.7)</td>
<td>47 (6.4)*</td>
<td>17 (2.2)**</td>
<td>13 (4)</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>94 (3.5)</td>
<td>18 (2.3)**</td>
<td>7 (1)*</td>
<td>63 (8.3)*</td>
<td>2 (0.6)*</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Alcohol abuse (&gt;80 g/day)</td>
<td>66 (2.4)</td>
<td>26 (3.4)**</td>
<td>21 (2.9)</td>
<td>5 (0.7)**</td>
<td>10 (3.1)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>57 (2.1)</td>
<td>17 (2.2)</td>
<td>15 (2.1)</td>
<td>15 (2)</td>
<td>10 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Previous cerebral hemorrhage</td>
<td>32 (1.2)</td>
<td>9 (1.2)</td>
<td>9 (1.2)</td>
<td>7 (0.9)</td>
<td>6 (1.9)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

*p < 0.001.
**p < 0.01.
***p < 0.05.
COPD: Chronic obstructive pulmonary disease.

Clinical features
There are no absolute criteria for the diagnosis of cardioembolic infarction, although the following is required: compatible clinical picture, recognition of an embolic heart disease, and exclusion of carotid and/or cerebral atherosclerosis or other cause for the stroke.

Certain clinical features are suggestive of cardioembolic stroke. These include sudden onset to maximal deficit, decreased level of consciousness at onset, Wernicke’s aphasia or global aphasia without hemiparesis, Valsalva maneuver at the time of stroke onset and co-occurrence of cerebral and systemic emboli [1–3,12–15]. In 4.7–12% of cases, cardioembolic infarctions show a rapid regression of symptoms (the spectacular shrinking deficit syndrome). This dramatic improvement of an initially severe neurological deficit may be due to distal migration of the embolus followed by recanalization of the occluded vessel [1].

In the posterior circulation, cardioembolism can produce Wallenberg’s syndrome, cerebellar infarcts, top-of-the-basilar syndrome, multilevel infaracts or infarcts in the posterior cerebral artery. Visual-field abnormalities, neglect and aphasia are also more common in cardioembolic than in non-cardioembolic stroke [1–4].

It should be noted that a lacunar clinical presentation (a lacunar infarct and especially multiple lacunar infarcts) make cardioembolic origin unlikely (Figure 2) [16].

Early differential diagnosis between cardioembolic & atherothrombotic infarctions
Clinical data exclusive of cardioembolic infarction or atherothrombotic infarction are lacking. A clinical study has shown that atrial fibrillation and sudden onset of symptoms were independently associated with cardioembolic stroke, whereas hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hyperlipidemia and age were significantly associated with atherothrombotic infarction [17]. Clinical features traditionally associated with cardioembolic stroke, such as seizures or headache were not predictors of cardioembolic infarction as shown in the studies of Ramirez-Lassepas et al. [18], Kittner et al. [19,20] and Caplan [21].

Diagnostic testing
Neuroimaging studies
Neuroimaging findings that support cardioembolic stroke include simultaneous or sequential strokes in different arterial territories. Owing to their large size, cardiac emboli flow to the intracranial vessels in most cases and cause massive, superficial, single large striatocapsular, or multiple infarcts in the middle cerebral artery. Therefore, cardioembolic infarctions predominate in the distribution territories of the carotid and the middle cerebral artery [13–15]. On the CT scan, bihemispheric combined
anterior and posterior circulation, or bilateral or multilevel posterior infarcts are suggestive of cardioembolism. MRI studies can increase the suspicion of cardioembolism by demonstrating lesions not apparent on CT scans [1].

Hemorrhagic transformation of an ischemic infarct and early recanalization of an occluded intracranial vessel are suggestive of a cardiac origin of the stroke [1–3]. Hemorrhagic transformation occurs in up to 71% of cardioembolic strokes (Figure 3). As many as 95% of hemorrhagic infarcts have a cardioembolic pathophysiological mechanism. Besides hemorrhagic transformation, secondary hematomas are unusual and are found in 0.8% of cases in the stroke registry of our hospital [4]. A common nomenclature divides hemorrhages into HI1, HI2, PH1, PH2 and remote PH. HI has been defined as a petechial infarction without space-occupying effect and PH was defined as a hemorrhage (coagulum) with mass effect. HIs comprise of two subtypes: HI1 (small petechiae) and HI2 (more confluent petechiae). Similarly, there are three subtypes of PH: PH1 (≤30% of the infarcted area with some mild space-occupying effect), PH2 (>30% of the infarcted area with significant space-occupying effect) and remote PH (clot remote from the infarcted area) [22]. The traditional explanation for hemorrhagic transformation is that the infarct is caused by blockage of a large artery by the thrombus; this blockage then causes local vascular spasm. Release of this local spasm and fragmentation of the thrombus allows the thrombus to migrate distally, exposing ischemic tissues and damaged vessel walls and capillaries to reperfusion. Arterial dissection at the site of impact of the thrombus is an alternative explanation.

Cardiac work-up studies
After a complete diagnostic work-up investigation, up to 30–38% of ischemic strokes remain with an undetermined cause, although in most of these cases an embolic mechanism is suspected. There exists a considerable amount of conflicting issues among experts regarding the extent of cardiac testing in acute stroke patients. All acute ischemic stroke patients must be evaluated with initial ECG and receive serial ECG. Moreover, 24-h Holter monitoring is necessary to identify potential sources of embolism [23–25]. However, 24-h Holter may not be sufficient for diagnosing paroxysmal atrial fibrillation and there is evidence supporting the value of prolonged cardiac monitoring. In a recent study by Gaillard et al., transtelephonic ECG monitoring increased the detection rate of paroxysmal atrial fibrillation in stroke and transient
ischemic attack (TIA) patients whose 24-h Holter result was negative, especially if they had frequent premature atrial ectopic beats, recent anterior circulation infarct on MRI, or both [26]. The implantation of subcutaneous devices for up to 14 months of rhythm monitoring increases the detection of paroxysmal atrial fibrillation [27].

Patients with lacunar stroke or with symptomatic ≥50% ipsilateral artery stenosis may not need extended cardiac monitoring or imaging. All patients with undetermined stroke after these studies with an embolic neuroimaging pattern should undergo transthoracic echocardiography by showing the passage of air microbubbles from the right to the left cardiac cavities after the intravenous administration of echo contrast. Although second harmonic imaging has an increased transthoracic echocardiography sensitivity, contrast transesophageal echocardiography remains the standard echocardiographic technique, particularly in young patients suffering from cryptogenic stroke. Transcranial Doppler (TCD) allows a first-line, noninvasive diagnosis of right-to-left shunt caused by a patent foramen ovale by detecting bubble signs in the middle cerebral artery after the injection of agitated saline in the antecubital vein. The most important limitation of contrast TCD is the absence of a temporal bone window in 10% of patients who suffer stroke, a fact that particularly affects the older population. However, TCD does not distinguish intracardiac from extracardiac shunts.

**Lacunar cardioembolic stroke**

Embolicgenic cardiopathy as the only demonstrable etiology has been found in 2.6–5% of lacunar infarctions [28,29], and its causative role in lacunar infarction is very rare. However, in very elderly patients aged ≥85 years compared with patients under the age of 85 years, the higher occurrence of atrial fibrillation (28.2 vs 8.7%; odds ratio [OR]: 3.77), and the lower prevalence of hypertension (61.5 vs 77.3%; OR: 0.35) and diabetes (7.7 vs 28.4%; OR: 0.16) indicates that the cardioembolic pathogenic mechanism may be more frequent than generally established for lacunar syndromes [30].

**Cardiac sources of embolus**

As shown in Box 1, the most common high-risk cardioembolic conditions in patients with cardioembolic infarction include atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated cardiomyopathy and mitral rheumatic stenosis [1,14,15]. Other major sources of cardioembolism are infective endocarditis, marantic endocarditis and atrial myxoma. Atrial septal aneurysm, atrial or ventricular septal defects, calcific aortic stenosis, and mitral annular calcification are other minor sources of cardioembolism [31]. However, patent foramen ovale, aortic arch atheroma and mitral annular calcification are emerging cardioembolic sources.

A patent foramen ovale is present in approximately 25% of the general population and can be found in up to 40% of younger patients with otherwise cryptogenic stroke (Figures 4 & 5) [32]. There is a higher risk of stroke with patent foramen ovale, especially when combined with atrial septal aneurysm. In a meta-analysis of case–control studies that examined the relative frequency of patent foramen ovale, atrial septal aneurysm or both, in all patients with ischemic stroke, cryptogenic stroke and known stroke cause, patent foramen ovale and atrial septal aneurysm were significantly associated with ischemic stroke in those younger than 55 years. It was concluded that further studies are needed to establish whether an association exists between patent foramen ovale and ischemic stroke in patients older than 55 years [33]. There is insufficient evidence to recommend warfarin routinely in patients with cryptogenic stroke and patent foramen ovale. There was no difference in stroke recurrence in cryptogenic stroke between patients with and without massive right-to-left shunt [34]. The American Heart Association, the American Stroke Association, the American Academy of Neurology [35,36] and the European Stroke Organization [37] recommend antiplatelet agents to prevent recurrent events while waiting for the results of ongoing clinical
trials regarding closure of patent foramen ovale. In clinical practice, aspirin is the recommended treatment for stroke patients with a patent foramen ovale, and indications of closure should be individualized and particularly considered only in young patients with recurrent stroke receiving medical treatment or when anticoagulant treatment is being considered.

Regarding complex aortic arch atheromatosis, in a review of 500 necropsies of patients with neurological diseases, ulcerated aortic plaques were documented in 62 out of 239 patients (26%) in whom stroke was the cause of death and in only 13 out of 261 patients (5%) who died as a result of other neurological conditions. Likewise, ulcerated aortic plaques were observed in 17 out of 28 patients (61%) with cerebral infarction of unknown etiology compared with 34 out of 155 patients (22%) in whom a cerebral infarction-attributable etiology was found [38].

The main emboligenic risk criteria for atheromatous plaques of the aortic arch include plaque thickness ≥4 mm and the presence of mobile components (Figure 6) [39].

It has recently been shown that complex atheromatous aortic plaques play a causative role in the recurrence of ischemic stroke in the subgroup of cerebral infarctions of undetermined etiology [40]. The efficacy of anticoagulation versus antiplatelet therapy in the prevention of stroke recurrence in patients with atherothrombosis of the aortic arch and a recent (<6 months) cerebral or peripheral embolic event is the objective of the ongoing Aortic Arch Related Cerebral Hazard (ARCH) trial from France.

The protective effect of statin therapy on the incidence of stroke and other embolic events in patients with severe thoracic aortic plaque was reported in a matched-paired analysis [41].

Mitral annular calcification is a chronic degenerative process characterized by calcium and lipid deposition in the fibrous support of the mitral valve. Mitral annular calcification has been cited as a possible source of cerebral embolism, with a relative risk of stroke of 2.1 in the Framingham Study independent of traditional risk factors for stroke [42]. In a recent study involving patients with ischemic stroke of uncertain etiology, dense mitral annular calcification was an important marker of aortic arch atherosclerosis with high risk of embolism [5]. In patients with clinically suspected embolic stroke of unknown etiology, mitral annular calcification should alert the clinician to the presence of advanced atherosclerosis in the proximal aorta as the embolic source.
Cardioembolic stroke is the subtype of cerebral infarction with the highest in-hospital mortality [1,43,44]. In our experience, and in agreement with the data of Caplan et al. [45], the in-hospital mortality rate in patients with cardioembolic infarction was 27.3% compared with 0.8% in patients with lacunar stroke and 21.7% in patients with atherothrombotic infarction [7]. Among patients with cerebral infarction, the mortality rate was 30% in patients with congestive heart failure, 22% in patients with atrial fibrillation and 18% in patients with COPD. In the subgroup of cardioembolic stroke, factors independently associated with in-hospital mortality were peripheral arterial disease (OR: 2.18), previous cerebral infarction (OR: 1.75) and congestive heart failure (OR: 1.71) (Table 2). In a logistic regression model that included demographic, clinical and outcome variables, age, congestive heart failure, hemiparesis and altered consciousness were significant predictors of cardioembolic stroke. However, when early recurrent embolism was added to the model, this variable was associated with the highest risk (OR: 33.5). The in-hospital mortality rate in early cardioembolic recurrence was 78% compared with 25.2% in the remaining cases.

Cardioembolic recurrence

The risk of early embolic recurrence in cerebral infarction varies between 1 and 10%. In the Cerebral Embolism Task Force, it was estimated that 12% of patients with a first-ever cardioembolic stroke would present a second embolism within the first 2 weeks [46]. In our experience, early embolic recurrence was observed in 24 out of 347 consecutive patients (6.9%) with cardioembolic infarction [47]. Embolism recurrence occurred within the first 7 days in 12 patients (50%). The mean time to recurrence was 12 days. Embolic recurrence at 30 days was also documented in five out of 81 patients (6.1%) with cardioembolic infarction and nonvalvular atrial fibrillation reported by Yamanouchi et al. [48], in 6% of cerebral infarcts in the study by Sacco et al. [49], in 3.3% of patients in the Stroke Data Bank [50] and in 4.4% of patients in the Lausanne Stroke Registry [51].

Risk factors for recurrent embolism are poorly recognized. In our series, alcohol abuse (OR: 21.8), hypertension in association with heart valve disease and atrial fibrillation (OR: 4.3), nausea and vomiting (OR: 3.7), and previous cerebral infarction (OR: 3.2) were significant risk factors. In addition to these four variables, cardiac events (tachyarrhythmia, heart failure or acute myocardial infarction that occurred as medical complications during the patient’s hospital stay) were selected in the multivariate model based on clinical, neuroimaging and outcome variables (OR: 4.25) [47].

Box 1. Type of heart disease and cardioembolic risk.

High risk of embolism
- Atrial fibrillation
- Acute myocardial infarction within the previous 6 weeks
- Mechanical valve prosthesis
- Mitral stenosis of rheumatic origin
- Atrial or ventricular thrombi
- Atrial myxoma and cardiac tumors
- Infectious/marantic endocarditis
- Complex aortic arch atheromatosis
- Dilated myocardopathy with ventricular ejection fraction <35%

Moderate/low risk of embolism
- Calcification of the mitral valve ring
- Patent foramen ovale
- Atrial septal aneurysm
- Calcified aortic stenosis
- Bioprosthetic valve
- Mitral valve prolapse
- Spontaneous echo contrast

Data taken from [4,6,12].

Prognostic importance of atrial fibrillation in cardioembolic & atherothrombotic infarctions

Atrial fibrillation is the main underlying heart disease in various series of cardioembolic infarction in industrialized countries [52–55]. Atrial fibrillation can also be found in atherothrombotic infarction, not only as an embolic etiology but as a marker of other conditions that lead to ischemic stroke, such as atherosclerosis. Patients presenting with atrial fibrillation may also have a noncardioembolic ischemic stroke since some risk factors are the same. It can therefore be considered an epiphenomenon or one of the clinical manifestations of atherosclerotic disease [56], so that not all cerebral infarcts in patients with atrial fibrillation are of cardioembolic origin [57]. In one of our group’s studies, atrial fibrillation was diagnosed in 16.5% of patients with atherothrombotic occlusion or an arterial stenosis >70%, which was presumably responsible for the cerebral infarct [8].

In patients with cardioembolic stroke, in-hospital mortality was 31.6% in those with atrial fibrillation and 14.8% in those without [8]. On the other hand, in patients with atherothrombotic stroke, in-hospital mortality was 29.3% in those...
with atrial fibrillation and 18.8% in those without atrial fibrillation (p < 0.04) [8]. It should be noted that the presence of atrial fibrillation was associated with a worse clinical outcome in both cardioembolic and atherothrombotic infarction, which may be due to a higher frequency of heart failure in the group of cardioembolic stroke and atrial fibrillation, and a higher frequency of ischemic heart disease in the group of atherothrombotic stroke and atrial fibrillation.

Chronic atrial fibrillation may cause a significant reduction in regional cerebral blood flow [58,59], although this decrease can be normalized with sinus rhythm after cardioversion [60]. The increase in mortality may also be explained by a more advanced age, greater size of the cerebral lesion or a higher initial intensity of focal neurological deficit in patients with atrial fibrillation [61,62].

Blood biomarkers

One promising field in neurovascular disease investigation is the use of blood biomarkers to guide stroke etiology diagnosis and classification. High levels of B-type natriuretic peptide (BNP), soluble receptor for advanced glycation end products and d-dimer were observed in patients with cardioembolic stroke. In a recent study, independent predictors of cardioembolic stroke included atrial fibrillation, other embolic cardiopathies, total anterior circulation infarction, serum BNP level >76 pg/ml and serum d-dimer concentration >0.96 µg/ml. Even among patients with transient symptoms (n = 155), a high serum BNP concentration identified cardioembolic etiology. A model combining clinical and biochemical data had a sensitivity of 66.5% and a specificity of 91.3% for predicting cardioembolism. Using a combination of serum biomarkers may be a feasible strategy to improve the diagnosis of cardioembolic stroke in the acute phase, thus rapidly guiding other diagnostic tests and accelerating the start of optimal secondary prevention therapy [63,64].

Special clinical conditions

Ischemic stroke in heart failure

Ischemic stroke in patients with heart failure is more severe and has a poor prognosis. In community studies, the prevalence of stroke and transient ischemic attack was higher in individuals with heart failure than in the general population. In the Framingham study, the adjusted risk of stroke associated with heart failure was 4.3 at 2 years follow-up [65].

Due to new epidemiological evidence, symptomatic heart failure with low ejection fraction and chronic myocardial infarction with ejection fraction of less than 28% were included as primary high-risk sources of embolic stroke [66]. The stroke mechanism in heart failure may be embolism or cerebral hypoperfusion. Heart failure was independently associated with stroke recurrence at 7 days (adjusted OR: 2.6) and at 90 days (OR: 2.4) [67].

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All brain infarctions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.33 (1.84–2.96)</td>
<td>0.000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.96 (1.33–2.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>1.56 (1.01–1.89)</td>
<td>0.044</td>
</tr>
<tr>
<td>Previous cerebral infarction</td>
<td>1.43 (1.07–1.89)</td>
<td>0.014</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.03–1.06)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.58 (0.39–0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Atherothrombotic infarct</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.87 (1.45–5.71)</td>
<td>0.003</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.80 (1.09–2.96)</td>
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<tr>
<td>Age</td>
<td>1.03 (1.01–1.05)</td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.53 (0.28–0.98)</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Cardioembolic infarction</strong></td>
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<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2.18 (1.17–4.05)</td>
<td>0.014</td>
</tr>
<tr>
<td>Previous cerebral infarction</td>
<td>1.75 (1.16–2.63)</td>
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<tr>
<td>Heart failure</td>
<td>1.71 (1.01–2.90)</td>
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<tr>
<td>Age</td>
<td>1.06 (1.04–1.08)</td>
<td>0.000</td>
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<tr>
<td><strong>Undetermined etiology</strong></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>3.68 (1.78–7.62)</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.01–1.09)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 2. Predictive value of cardiovascular risk factors for in-hospital death in the different stroke subtypes in the Sagrat Cor Hospital of Barcelona Stroke Registry.

Data taken from [12].

Neurological complications after cardiothoracic surgery

Neurological complications in orthotopic heart transplantation represent a major cause of morbidity and mortality despite successful transplant [68]. During the perioperative period, the frequency of cerebrovascular complications ranges between 5 and 11%, with ischemic stroke being the most common. In a recent clinical series of 314 patients undergoing heart transplant and followed for a mean of 54 months, 22 (7%) presented an acute stroke (hemorrhagic stroke: 12%; transient ischemic attack: 28%; ischemic stroke: 60%) [31]. Acute stroke occurred early postoperatively (<2 weeks) in 20% of patients and late in 80%. The etiological classification was large-artery atherosclerosis (15.4%), cardioembolism (14.4%), small-vessel disease (15.4%), unusual causes (15.4%) and undetermined cause (38.4%). The only independent predictor of acute stroke was a prior acute stroke event (OR: 8.2; p < 0.02). The estimated risk of cerebrovascular disease (hemorrhagic stroke, TIA, ischemic stroke) at 5 years following cardiac transplantation was greater in patients with a history of acute stroke (4.1%) than in those without previous [69,70].
stroke (1.1%). Acute stroke is a relatively frequent complication after cardiac transplantation (7%) and usually occurs in the late postoperative period. A previous history of stroke is an important risk factor for recurrent stroke after transplantation [69].

The reported incidence of symptomatic stroke after coronary artery bypass grafting is between 0.8 and 5.2%. Acute stroke after percutaneous coronary intervention, although rare, is associated with high rates of mortality and morbidity. The incidence of stroke and TIA range from 0.27 to 0.50% [70]. Neurological complications after cardiac catheterization are infrequent, occurring in approximately less than 0.5% of patients [71].

**Treatment**

**Thrombolysis**

Intravenous thrombolysis with tissue plasminogen activator (tPA) within 4.5 h of the onset of symptoms significantly improves clinical outcome in patients with acute ischemic stroke [72,73]. Pharmacological intra-arterial thrombolysis has been shown to be effective until 6 h after middle cerebral artery occlusion and offers a higher rate of recanalization compared with intravenous thrombolysis [74,75].

The more recent advances in reperfusion therapies have been carried out in mechanical embolus disruption or removal. Mechanical devices are being used in clinical practice for patients who are ineligible for tPA or who have failed to respond to intravenous tPA [76]. Experimental studies have revealed that lytic susceptibility and penetration of thrombolytic agents into the thrombus depends on the specific structural aspects of clots. Old, platelet-rich and well-organized thrombi formed under flow conditions have been shown to be more resistant to thrombolysis than fresh fibrin- and red cell-rich clots formed under conditions of stasis [77]. In humans, thromboembolic arterial occlusions may originate from various proximal sources, including venous sites, mural cardiac thrombi, or atherosclerotic lesions within or proximal to the affected vessel. The cardiac source of the clot probably represents the stroke subtype with more uniform fibrin-rich clots and higher efficacy of thrombolysis. However, results of large clinical studies and main randomized clinical trials of intravenous thrombolysis have demonstrated no significant difference in the final outcome of tPA-treated patients based on confirmed stroke mechanism [72,73]. This is probably because cardioembolic strokes are caused by large clots, are more severe strokes, and hence they may not be as easily thrombolyzed by intravenous tPA, even though the clot morphology may be favorable. Patients with cardioembolic stroke treated with thrombolysis are not at increased risk of hemorrhagic transformation.

**Anticoagulation: cardiac procedures**

Not all cardioembolic strokes should be treated with anticoagulation. Cardiac indications for anticoagulation comprise atrial fibrillation, mural thrombi, prosthetic valves and marantic endocarditis. Anticoagulation is not indicated for infectious endocarditis. Antiplatelets are recommended in patent foramen ovale, mitral annular calcification and mitral valve prolapse. Treatment of cardiac tumors requires surgery.

Oral anticoagulation (international normalized ratio: 2–3) is indicated for secondary prevention in most patients with cardioembolic ischemic stroke without contraindications for anticoagulant therapy, such as falls, poor compliance, uncontrolled epilepsy or gastrointestinal bleeding. Anticoagulation should be started as soon as possible, as it is safe even in moderate-acute strokes [78,79]. There is evidence from animal models and clinical studies that anticoagulation with unfractionated heparin (UFH) is associated with a better outcome in acute ischemic stroke, mediated in part by its anti-inflammatory properties [80]. Most stroke experts do not recommend acute anticoagulation in acute ischemic stroke. However, the Rapid Anticoagulation Prevents Ischemic Damage (RAPID) trial was a randomized trial evaluating immediate anticoagulation in ischemic stroke [81]. It was able to show a trend toward more effective prevention of stroke recurrence with UFH (0%) than aspirin (8.6%; p = 0.09) and without an increment in serious bleeding (8.6% for aspirin, 6.3% for UFH; p = 0.71). Later, in the prethrombolytic era, a randomized clinical trial compared the effects of UFH and placebo in the first 3 h after stroke onset [82]. The trial included 418 patients with an ischemic nonlacunar stroke. In the group treated with UFH there was a better outcome at 3 months (self-independent patients, 38.9 vs 28.6%), fewer deaths (16.8 vs 21.9%), and more symptomatic brain hemorrhages (6.2 vs 1.4%) as well as and more major extracerebral bleedings (2.9 vs 1.4%). This is the first randomized trial to show that UFH administered in the first 3 h after a non-lacunar ischemic stroke is effective in reducing dependence when compared with placebo.

In overall terms, the incidence of stroke in individuals with nonvalvular atrial fibrillation is estimated to be two- to sevenfold higher that in subjects without atrial fibrillation and, for those with valvular atrial fibrillation, the risk of stroke is 17-times greater that in age-matched controls. For nonvalvular atrial fibrillation, the risk of stroke ranges widely depending on the presence of certain other characteristics (Table 3) [83–88]. Oral anticoagulation reduces the risk of recurrent stroke in patients with nonvalvular atrial fibrillation regardless the type (permanent, chronic or paroxysmal). Several risk-stratification schemes have been developed in order to maximize the benefits of anti-thrombotic treatment to prevent the risk of first stroke in individual patients (Table 3). Primary-prevention patients whose stroke risk exceeds 4 per 100 patient-years on aspirin benefit from oral anticoagulation. Stroke-prone patients are reliably identified by a CHADS score >3, and they have an average risk of 5.5 strokes per 100 patient-years on aspirin. High-risk primary-prevention patients are less well identified with the other schemes described in the Table 3. Yet all schemes are equally sensitive to detect low-risk patients whose stroke rate is 1.4 or lower per 100 patient-years of aspirin. Oral anticoagulation is more effective in patients with atrial fibrillation who have one or more risk factors, such as previous systemic embolism, age over 75 years, high blood pressure or poor left ventricular function.

Dabigatran is a potent, direct, competitive inhibitor of thrombin that, like ximelagatran, does not require regular monitoring.
Table 3. Stroke risk stratification schemes in patients with nonvalvular atrial fibrillation.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Low risk of stroke</th>
<th>Moderate risk or stroke</th>
<th>High risk or stroke</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation Investigators</td>
<td>Not moderate/high risk</td>
<td>Age &gt;65 years of age, not high risk</td>
<td>Prior ischemia, high BP, DM</td>
<td>[70]</td>
</tr>
<tr>
<td>SPAF III study</td>
<td>Not moderate/high risk</td>
<td>High BP, not high risk</td>
<td>Prior ischemia, female &gt;75 years of age, CHF, LV &lt;25%, systolic BP &gt;160</td>
<td>[71]</td>
</tr>
<tr>
<td>The seventh ACCP Conference on Anti-thrombotic and Thrombolytic Therapy</td>
<td>Not moderate/high risk</td>
<td>One of: 65–75 years of age, DM, CAD and not high risk</td>
<td>Prior ischemia, high BP, CHF, &gt;75 years of age, or ≥2 moderate risk factors</td>
<td>[72,73]</td>
</tr>
<tr>
<td>CHADS2 scoring system¹</td>
<td>Score: 0</td>
<td>Score: 1</td>
<td>Score: ≥2</td>
<td>[74]</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td>Score: +6 for prior ischemia; 0–4 for BP; +4 for DM; +0–10 for age; 6 for female</td>
<td>Predicted 5-year risk of stroke ranges between 5% for 0–1 points and 75% for 31 points</td>
<td>[75]</td>
<td></td>
</tr>
</tbody>
</table>

¹Assigns 1 point each for CHF, high BP, age 75 years or older and diabetes, and 2 points for a previous stroke or transient ischemic attack. ACCP: American College of Chest Physicians; BP: Blood pressure; CAD: Coronary artery disease; CHF: Congestive heart failure; DM: Diabetes mellitus; LV: Left ventricular fractional shortening; SPAF: Stroke Prevention in Atrial Fibrillation.

Dabigatran has been shown to be noninferior to warfarin in the prevention of stroke or systemic embolism [89].

Left atrial appendage occlusion and ablation procedures for atrial fibrillation are other possible therapeutic cardiac options in selected patients.

In summary, cerebral cardioembolism is an important topic in the frontier between cardiology and vascular neurology, it occurs frequently in daily practice, and has a high impact on patients, healthcare systems and society.

**Expert commentary**

Stroke is the second leading cause of death worldwide and is a major determinant of adult disability. Cardioembolic infarction occurs in 25% of all cerebral infarcts. Cardioembolic stroke is the most severe ischemic stroke subtype, with a high risk of early embolic recurrence and the highest in-hospital mortality. Lacunar clinical presentations, a lacunar infarct and especially multiple lacunar infarcts make cardioembolic origins unlikely. The most common high-risk cardioembolic conditions comprise of atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated myocardialopathy and mitral rheumatic stenosis. Patent foramen ovale and complex atheromatosis of the aortic arch are potentially emerging cardioembolic etiologies. Mitral annular calcification can be a marker of complex aortic atheroma in patients with stroke of uncertain etiology. High levels of serum BNP and d-dimer may be observed in patients with cardioembolic stroke. Ischemic stroke in patients with heart failure is more severe and has a poor prognosis. Acute stroke prior to cardiac transplantation increases the risk of acute stroke after this procedure. The cardiac source of the clot probably represent the stroke subtype with more uniform fibrin-rich clots and higher efficacy of thrombolysis. In patients without contraindications, oral anticoagulation is recommended in most cardioembolic strokes for secondary prevention. Dabigatran has been shown to be noninferior to warfarin in the prevention of stroke or systemic embolism. Published guidelines and stroke-stratification schema for atrial fibrillation patients serve as guidance for clinicians to initiate appropriate thromboprophylaxis therapy for these patients in the hope of reducing the incidence of stroke.

**Five-year view**

There are still some aspects of cardioembolic stroke that merit further investigation, such as:

- Clinical and prognostic characteristics of lacunar infarction of cardioembolic cause;
- Individualized analysis of risk factors, clinical features and outcome in very old patients with cardioembolic stroke;
- Definition of when closure of a patent foramen ovale is indicated;
- Assessment of the efficacy of antiplatelet treatment or anticoagulation in preventing stroke recurrence in complex aortic atheromatosis;
- Genome-wide association studies will contribute to the identification of additional genes, novel pathways; and eventually novel therapeutic approaches to cardioembolic stroke;
- Biomarkers related to cardioembolic stroke etiology (such as BNP and d-dimer proteins) might allow the rapid guidance of other diagnostic tests and accelerate the development of an optimal secondary prevention;
- A risk of hemorrhage prediction scheme is needed for stroke patients on oral anticoagulation for nonvalvular atrial fibrillation who are found to have cerebral microbleeds on neuroimaging;
- The development of novel anticoagulants may revolutionize our approach to providing thromboprophylaxis in atrial fibrillation;
- Advances in cell-based therapeutics, regenerative medicine and tissue engineering are raising the possibility of replacing damaged neurons or coaxing neuronal circuits to regenerate;
- Ongoing trials may provide answers to these questions.
A decrease in the prevalence of cerebral infarcts of undetermined etiology and an increase in the prevalence of cardioembolic strokes may be observed in relation to a more systematic use of cardiac work-up studies and blood biomarkers in the next 5 years.

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**Key issues**
- Stroke is a leading cause of disability in the world.
- Cardioembolic stroke is the most frequent ischemic subtype in very old patients (>85 years of age).
- Lacunar clinical presentations, a lacunar infarct and especially multiple lacunar infarcts, make cardioembolic origin unlikely.
- The most common high-risk cardioembolic conditions are atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated cardiomyopathy and mitral rheumatic stenosis.
- Aspirin is the recommended treatment in stroke patients with a patent foramen ovale. There is insufficient evidence to recommend warfarin routinely in patients with cryptogenic stroke and patent foramen ovale.
- Prolonged cardiac rhythm monitoring increases the detection of paroxysmal atrial fibrillation.
- All patients with an undetermined cause of stroke and with an embolic pattern on neuroimaging studies, should undergo transthoracic echocardiography followed by transesophageal echocardiography if findings of the transthoracic route are inconclusion.
- Mitral annular calcification can be a marker of complex atheromatosis in the aortic arch.
- The main criteria of embolic risk associated with aortic atheromatosis are plaque thickness ≥4 mm and the presence of mobile components.
- Statin therapy has a protective effect on the incidence of stroke and other embolic events in patients with severe thoracic aortic plaque.
- Serum biomarkers (B-type natriuretic peptide and d-dimer) might become an additional diagnostic tool in cardioembolic stroke.
- Ischemic stroke in patients with heart failure is more severe and has a poor prognosis.
- A previous history of stroke is an important risk factor to suffer a recurrent stroke after heart transplantation.
- Oral anticoagulation is indicated in most cardioembolic ischemic strokes for secondary prevention (atrial fibrillation, mural thrombi, prosthetic valves and marantic endocarditis). Anticoagulation is not indicated for infectious endocarditis. Antiplatelets are recommended in patent foramen ovale, mitral annular calcification and mitral valve prolapse. Treatment of cardiac tumors requires surgery.
- Dabigatran is noninferior to warfarin in the prevention of stroke or systemic embolism.
- Cardiac source of the clot might probably represent the stroke subtype with more uniform fibrin-rich clots and higher efficacy of thrombolysis. However, results of randomized clinical trials of intravenous thrombolysis have demonstrated no significant difference in final outcome in tPA-treated patients based on confirmed stroke mechanism.

**References**
Papers of special note have been highlighted as:
- of interest
- of considerable interest
2. Comprehensive review on cardioembolic stroke.

**Financial & competing interests disclosure**
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No writing assistance was utilized in the production of this manuscript.


• Didactic and complete review on the mechanisms of cardioembolic stroke.


• This multicenter clinical study demonstrates that essential infarctions associated with patent foramen ovale are less severe, have a lower number of recurrences and can be treated with aspirin.


• Current guidelines of the American Academy of Neurology on secondary prevention of ischemic stroke.


• Current guidelines of the European Stroke Organization on the management of acute stroke and secondary prevention.


Clinical study demonstrating clinical factors associated with early embolic recurrence in cardioembolic stroke.


Complete review of blood biomarkers in acute stroke.


Ogawa A, Mori E, Minematsu K et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke* 38, 2633–2639 (2007).


Current guidelines of the American Heart Association for the management of acute ischemic stroke.


- Demonstrates the efficacy of dabigatran in the prevention of thromboembolic events in patients with atrial fibrillation.