Adverse outcomes following percutaneous transcatheter interventions

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Chapter 1

Silent cerebral infarcts in relation to cardiac disease and procedures.


ABSTRACT

The occurrence of clinically silent cerebral infarcts (SCIs) in individuals affected by cardiac disease and after invasive cardiac procedures is frequently reported. Indeed, atrial fibrillation, left ventricular thrombus formation, cardiomyopathy, and patent foramen ovale have all been associated with SCIs. Furthermore, postprocedural SCIs have been observed after left cardiac catheterization, transcatheter aortic valve implantation, CABG surgery, pulmonary vein isolation, and closure of patent foramen ovale. Such SCIs are often described as a precursors for symptomatic stroke and are associated with cognitive decline, dementia, and depression. Increased recognition of SCIs might advance our understanding of their relationship with heart disease and invasive cardiac procedures, facilitate further improvement of therapies or techniques aimed at preventing their occurrence and, therefore, decrease the risk of adverse neurological outcomes. In this Review, we provide an overview of the occurrence and clinical significance of, and the available diagnostic modalities for, SCIs related to cardiac disease and associated invasive cardiac procedures.
INTRODUCTION

Cardiac disease and related invasive interventions are potential causes of cerebral embolic events. Cardioembolic stroke is the subtype of stroke with the highest in-hospital mortality of approximately 20%.1,2 Improvements in anticoagulation therapy and interventional cardiology techniques have led to a decrease in the incidence of acute ischaemic stroke; however, silent cerebral infarcts (SCIs) are increasingly observed and are much more prevalent than symptomatic stroke.3

SCIs are described as parenchymal lesions that have MRI characteristics of a previous infarct event, but are not associated with acute clinical signs or symptoms of stroke or transient ischaemic attack (TIA).4 Advancements in MRI have resulted in increased detection and awareness of such lesions.3 The majority of SCIs are located in the subcortex—the region of the brain directly below the cerebral cortex that contains the thalamus, hypothalamus, cerebellum, and brain stem—and are commonly called asymptomatic lacunar infarcts.5 SCIs have been detected in 8–28% of the general population,6,7 and in 38% of patients with ischaemic stroke,8,9 with the incidence of SCI strongly increasing with age.10

SCIs have been associated with atrial fibrillation (AF), cardiomyopathies, patent foramen ovale (PFO), catherization, transcatheter aortic valve implantation (TAVI), CABG surgery, pulmonary vein isolation (PVI) and PFO closure. In addition to the settings of cardiac disease and the interventional procedures used to manage them, SCIs have been observed in the context of hypertension and indicators of cerebral small-vessel diseases, including brain white matter abnormalities and lacunar stroke.11,12 Indeed, accumulating evidence implicates SCIs in cognitive decline, dementia, and depression.13–16 Furthermore, several studies have demonstrated that SCIs have important prognostic implications for risk of future stroke. For example, in the Rotterdam Scan Study,17 the presence of SCIs was associated with a more than threefold increase in the risk of stroke, independently of other risk factors. SCIs can, therefore, be considered precursors of ischaemic stroke, and potentially enable the identification of patients at high-risk of this condition. Consequently, detection of SCIs and treatment of these high-risk patients might prevent or reduce the large burden of cardioembolic stroke. The relationships between cardiac diseases, cardiac procedures, SCIs, and neurological conditions are summarized in Figure 1.

In this Review, we introduce the imaging technologies that can be used to diagnose SCIs. However, we focus our discussion on the association between SCIs and various cardiovascular diseases and invasive procedures used to treat cardiac diseases. We also comment on the clinical significance of these relationships.
Figure 1. Summary of cardioembolic heart diseases and cardiac procedures that have been associated with silent cerebral infarcts.

The central image provides an example of small hyperintense lesions that indicate silent cerebral infarcts (arrows), visualized using fluid-attenuated inversion recovery MRI. Such lesions have been associated with forms of cardioembolic heart disease and cardiac intervention procedures. Silent cerebral infarcts are increasingly recognized as a contributing factor in various neurological conditions. Therefore, approaches to prevent or treat SCIs in patients with cardiovascular disease might reduce the risk of these outcomes.

DIAGNOSTIC NEUROIMAGING MODALITIES

SCIs are characterised by an infarction in the territory of one perforating arteriole with a threshold size of ≥3 mm. Such infarcts can be visualized on CT images as hypodense lesions, and when using MRI as hyperintense lesions on T2-weighted images. Improvements in MRI techniques, including stronger field magnets, thinner slices, and modified pulse sequences, have resulted in a higher sensitivity for detection of SCIs compared with CT. Indeed, a number of MRI techniques are now available that enable detection of SCIs, including diffusion-weighted MRI (DWI) for identification of acute ischaemic lesions, and T2-weighted imaging and fluid-attenuation inversion recovery (FLAIR) MRI for visualization of chronic SCIs. A wide variety of diagnostic criteria can be used for the evaluation of SCIs depending on the MRI sequences used. For example, some studies classified lesions with ≥3 mm in diameter as potential SCI, whereas others did not take diameters into account. Moreover, definitions in MRI signal characteristics are not standardized. These difference in diagnostic criteria limit the capacity to compare data between studies.

DWI is the most-sensitive technique for visualization and quantification of acute cerebral ischaemia. Acute ischaemic cerebral lesions are detectable by MRI owing to changes in the free motion of H₂O molecules (diffusion restriction) caused by the acute ischaemia, which is observed as an hyperintense, bright signal on diffusion-weighted...
images, and as low value on apparent diffusion coefficient maps. These signals usually disappear within 14 days after onset of ischaemia.

When assessing SCIs, these lesions must be distinguished from dilated Virchow–Robin spaces, which can be challenging using neuroimaging, particularly in instances when these MRI features coexist. Virchow–Robin spaces are fluid-filled perivascular canals that typically follow the course of a blood vessel through the grey or white matter, have a similar signal intensity to cerebrospinal fluid on all MRI pulse sequences, and are generally <3 mm in diameter. Old SCI lesions (>14 days) and cerebrospinal fluid both have hyperintense signals by T2-weighted MRI and DWI. According to a recent consensus statement by Wardlaw and colleagues aimed at providing universal definitions to be used in both research and clinical settings, the minimum neuroimaging examination for assessment of SCIs should include DWI, FLAIR MRI, and T2-weighted imaging.

**CARDIOVASCULAR DISEASE AND SCIS**

**Atrial fibrillation**

Left atrial thrombus formation as a result of AF is the most-common cause of thrombo-embolic stroke and accounts for >45% of cardiogenic thromboemboli. AF is associated with a twofold increase in stroke incidence, an association observed in patients with either paroxysmal or chronic AF. In addition, in a large population based post-mortem study (n = 966), AF was identified as an independent predictor of SCIs (OR 2.46, 95% CI 1.07–5.68). This finding was confirmed in the Framingham Offspring Study, in which AF was associated with an increased risk of SCIs detected using MRI (OR 2.16, 95% CI 1.07–4.40). Moreover, various studies have shown that AF is associated with an increased incidence of SCIs (Table 1).

In a longitudinal observational study, patients aged <60 years and with type 2 diabetes mellitus and subclinical AF had an increased prevalence of SCIs at baseline MRI assessment compared with patients who had type 2 diabetes and no diagnosed subclinical AF (61% versus 29%; P <0.01). Furthermore, the patients with subclinical AF had a higher incidence of ischaemic stroke than those without silent AF (17.3% versus 5.9%; P <0.01). In a prospective pilot study by Neumann and colleagues, SCIs were observed in 12.3% of the patients with symptomatic and drug-refractory paroxysmal or persistent AF (with no history of stroke) before pulmonary vein isolation.

The correlation between AF and cognitive impairment, dementia and Alzheimer disease has been assessed in several studies. In a meta-analysis, AF was independently associated with an increased risk of incident dementia (HR 1.42; 95% CI 1.17–1.72; P <0.001). Furthermore, in a large community-based cohort, the cumulative rate of dementia was 2.7% at 1 year and 10.5% at 5 years after diagnosis of AF in patients with-
out evidence of cognitive dysfunction or stroke at the time of onset. 37 Subsequently, SCIs have been postulated to underlie pathophysiological mechanisms related to these observations, based on their association with both AF and dementia. 37

### Table 1. Associations between cardiac diseases and SCIs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reference</th>
<th>Study design (n)</th>
<th>Anticoagulation therapy (%)</th>
<th>Imaging modality</th>
<th>Rate of SCIs (%)</th>
<th>Rate of stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Galta et al. (2013)</td>
<td>Case–control (90 paroxysmal AF, 90 persistent AF)</td>
<td>Aspirin: 24, OAC: 66</td>
<td>MRI</td>
<td>Paroxysmal AF: 89</td>
<td>Persistent AF: 92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None: 11</td>
<td></td>
<td>Controls: 46</td>
<td>46</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Patients with previous CVA or TIA were excluded</td>
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<td></td>
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<td></td>
<td></td>
<td>29</td>
<td>3-year follow-up</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>Kobayashi et al. (2012)</td>
<td>Case–control (71 with AF, 71 controls)</td>
<td>Aspirin: 55, OAC: 31</td>
<td>MRI</td>
<td>AF: 90 Controls: 69</td>
<td>Patients with previous CVA or TIA were excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.3</td>
<td>Patients with previous CVA were excluded</td>
</tr>
<tr>
<td>Symptomatic and drug-refractory paroxysmal or persistent AF</td>
<td>Neumann et al. (2011)</td>
<td>Prospective pilot study (45 cryoballoon ablation, 44 radiofrequency energy technique)</td>
<td>Aspirin: 25, Clopidogrel: 1</td>
<td>MRI</td>
<td>NA CT</td>
<td>14 (at baseline, of whom 14% had additional SCIs at 2-year follow-up)</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>Sato et al. (2004)</td>
<td>Case–control (212 with AF, 78 controls)</td>
<td>None in the first year</td>
<td>MRI</td>
<td>AF: 86 Controls: 54</td>
<td>20 (at 12-month follow-up, 21% of the patients with AF had new SCIs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At 12-month follow-up, 21% of the patients with AF had new SCIs</td>
<td></td>
</tr>
<tr>
<td>Nonvalvular AF with history (=3 months) of ischaemic stroke or TIA</td>
<td>EAPT Study Group (1996)</td>
<td>Double-blind RCT of OAC treatment versus aspirin or placebo (n = 886)</td>
<td>NA CT</td>
<td>15 (on baseline CT)</td>
<td>7* (3-year follow-up)</td>
<td></td>
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<td></td>
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<td>(3-year follow-up)</td>
<td></td>
</tr>
<tr>
<td>Nonvalvular AF without history of stroke or TIA</td>
<td>Ezekowitz et al. (1995)</td>
<td>RCT of warfarin versus placebo (n = 516)</td>
<td>NA CT</td>
<td>15 (on baseline CT)</td>
<td>7* (3-year follow-up)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-year follow-up)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls: 4</td>
<td>Controls: 4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with previous CVA or TIA were excluded</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy with LVEF &lt;20% being evaluated for heart transplantation</td>
<td>Siachos et al. (2005)</td>
<td>Observational cohort (n = 117)</td>
<td>Aspirin: 26, OAC: 27</td>
<td>MRI</td>
<td>CT or MRI</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls: 6</td>
<td>Patients with previous CVA or TIA were excluded</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td>(in entire cohort of 1,100 participants)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clergeau et al. (2005)</td>
<td>Case–control (15 with PFO, 45 without PFO)</td>
<td>NA MRI</td>
<td>PFO: 33 No PFO: 2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*In the 307 patients for whom a baseline and termination scan was available. Abbreviations: AF, atrial fibrillation; ASA, aspirin; CVA, cerebrovascular accident; DCM, dilated cardiomyopathy; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; NA, not available; OAC, oral anticoagulants; PFO, patent foramen ovale; RCT, randomized controlled trial; SCIs, silent cerebral infarcts; TIA, transient ischemic attack; VKA, vitamin K antagonist.

### Left ventricular thrombus formation

Left ventricular (LV) thrombus formation after myocardial infarction carries the risk of systemic thromboembolism, particularly in the cerebral circulation. In a meta-analysis of 11 studies, including 856 patients with anterior myocardial infarction, an odds ratio of 5.5 (95% CI 3.0–9.8) for embolic events was reported.38 Although LV thrombus formation is known to be associated with an increased embolic risk, no data are currently available on the occurrence of SCIs in patients with this condition. Nonetheless, in the ongoing,
randomized, controlled LV-THROMBUS study, two anticoagulant regimens for the treatment of left ventricular thrombus after myocardial infarction are being compared. The occurrence of SCIs is being recorded over time using serial MRI measurements, enabling investigation of the potential role of SCIs as precursors for stroke and cognitive dysfunction.

**Cardiomyopathy**

Heart failure is known to be associated with an increased risk of thromboembolism, with the reported rate of stroke in heart failure treatment trials varying from 1.8% to 2.4% per year. Siachos and colleagues were the first to report a 34% prevalence of SCIs in patients with advanced heart failure (LV ejection fraction [LVEF] <20%) being evaluated for heart transplantation (Table 1), suggesting the rate of subclinical infarcts is far higher than that of clinically manifest stroke. The causes of heart failure can be stratified into ischaemic and nonischaemic cardiomyopathies, with dilated cardiomyopathy being the most-common type of nonischaemic cardiomyopathy. The underlying mechanisms predisposing patients with dilated cardiomyopathy to the increased risk of emboli formation include low cardiac output, with subsequent stasis of blood in the dilated chamber, and an altered coagulation status.

In a case–control study, patients (n = 72) with ischaemic or nonischaemic dilated cardiomyopathy, but no history of stroke or TIA, had a 35% prevalence of MRI-detected SCIs. This prevalence of SCIs was significantly higher than that reported in the control group comprising healthy individuals (35% versus 3.6%; P <0.01). In a subsequent publication, the same investigators reported that 27% of the 26 patients with nonischaemic dilated cardiomyopathy assessed in this study had SCIs (Table 1). Ischaemic cardiomyopathy was also associated with an increased risk of thromboembolism; SCIs were detected in 39% of the 46 patients with ischaemic cardiomyopathy, which was markedly higher than the frequency observed in patients with nonischaemic cardiomyopathy and the age-matched controls (27% and 3.6%, respectively). In ischaemic cardiomyopathy, the mechanisms leading to an increased risk of thromboembolism are similar to those described in dilated cardiomyopathy, but with the additional risk factor of atherosclerosis. Independent risk factors associated with SCIs in patients with cardiomyopathy include impaired LV function, restrictive diastolic filling patterns on echocardiography, left atrial and aortic spontaneous echo contrast, and complex or calcified atherosclerotic lesions in the aorta.

**Patent foramen ovale**

Currently, whether a causal relationship exists between paradoxical emboli resulting from a patent foramen ovale (PFO) and cryptogenic stroke, a subtype (30–40%) of ischaemic strokes for which no well-defined underlying pathological mechanism is found,
Chapter 1

is a subject of debate. Nevertheless, investigators in various observational studies have reported an increased frequency of PFO in patients with cryptogenic stroke. Interestingly, a cross-sectional analysis of patients with cryptogenic stroke (or TIA) and PFO included in the Tufts PFO registry, reported a 17% prevalence of SCIs on MRI, suggesting that an association between PFO, SCIs, and stroke might exist.

Several pathophysiological mechanisms are postulated to contribute to cerebral emboli formation in patients with PFO. One hypothesis is that paradoxical emboli result from venous emboli travelling through the right–left shunt of the PFO into the left atrial circulation, thereby avoiding filtration by the lungs. This theory is supported by the findings of a prospective study by Clergeau and colleagues, who identified PFO as an independent predictor of SCIs in patients with pulmonary embolism. The reported prevalence of SCIs in patients with pulmonary embolism and PFO was significantly higher than in patients with pulmonary embolism without a PFO (33.3% versus 2.2%; \( P = 0.003 \); Table 1). However, only one patient in the study, who was found to have SCIs, experienced a stroke. Large studies with longer follow-up are needed to investigate this association further.

Other speculative mechanisms for cerebral emboli in patients with PFO include thrombus formation within the redundant interatrial tissue, particularly in patients with atrial septal aneurysm, and atrial arrhythmias resulting from PFO. The results of case–control studies suggest that the prevalence of PFO and atrial septal aneurysm is increased in patients suffering from cryptogenic stroke. In particular, the combination of a PFO and atrial septal aneurysm is thought to increase the risk of paradoxical emboli owing to compounded greater right–left shunt. Contrary to these findings, prospective and population-based studies have shown that the presence of PFO alone was not associated with ischaemic stroke, suggesting that concomitant venous thromboembolism would have to be present. In a study conducted by di Tullio and colleagues, no significant difference in the rates of SCI and were observed in patients with PFO compared with control individuals.

CARDIAC PROCEDURES AND SCIS

The heart–brain relationship and the outcomes of invasive procedures used in interventional cardiology have been investigated in an increasing number of studies. In general, such studies have shown an increased postprocedural prevalence of SCIs (Table 2). In addition to DWI, noninvasive transcranial Doppler (TCD) sonography has been used in a research setting to assess the occurrence of microembolisms in real-time during cardiac procedures. TCD sonography allows the detection of both gaseous and solid microemboli, entering the intracranial vessels of the circle of Willis, which are visualized as high-intensity transient signals.
Silent cerebral infarcts in relation to cardiac disease and procedures

Table 2. Associations between interventional cardiac procedures and SCIs

<table>
<thead>
<tr>
<th>Procedure and disease</th>
<th>Reference</th>
<th>Study design (n)</th>
<th>Access route</th>
<th>Imaging modality</th>
<th>Rate of SCIs (%)</th>
<th>Rate of stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheterization</strong></td>
<td></td>
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</tr>
<tr>
<td>CAD</td>
<td>Dhi et al. (2013)72</td>
<td>Prospective comparative study (115 left cardiac catheterisation, 56 MDCT)</td>
<td>Radial or femoral</td>
<td>MRI or MDCT</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Hamon et al. (2012)73</td>
<td>Observational (272 in phase I study, 102 in phase II study)</td>
<td>Radial or femoral</td>
<td>MRI</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>CAD</td>
<td>Kim et al. (2012)74</td>
<td>Observational</td>
<td>Radial or femoral</td>
<td>MRI</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>CAD</td>
<td>Kim et al. (2011)75</td>
<td>Observational (197)</td>
<td>Radial or femoral</td>
<td>MRI</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>PPVI patients with ACS</td>
<td>Mural et al. (2008)76</td>
<td>Observational (75)</td>
<td>Radial or femoral</td>
<td>MRI</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Hamon et al. (2007)77</td>
<td>Observational (41)</td>
<td>Radial</td>
<td>MRI</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Hamon et al. (2006)78</td>
<td>Observational (46)</td>
<td>Femoral</td>
<td>MRI</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Patients with CAD undergoing diagnostic and interventional catheterization</td>
<td>Büsing et al. (2005)79</td>
<td>Observational (48)</td>
<td>Femoral</td>
<td>MRI</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>CAD</td>
<td>Lund et al. (2005)80</td>
<td>Observational (47)</td>
<td>Radial or femoral</td>
<td>MRI</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Omran et al. (2003)81</td>
<td>Observational (101) or without [51] passage through the aortic valve</td>
<td>Femoral</td>
<td>MRI</td>
<td>19 and 3, respectively</td>
<td>3</td>
</tr>
<tr>
<td><strong>TAVI</strong></td>
<td></td>
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</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Ghanem et al. (2013)82</td>
<td>Observational pilot study (61)</td>
<td>Transfemoral</td>
<td>MRI</td>
<td>72*</td>
<td>7</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Fairbairn et al. (2012)83</td>
<td>Observational (51)</td>
<td>Femoral or subclavian</td>
<td>MRI</td>
<td>77</td>
<td>6</td>
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<tr>
<td>Aortic valve stenosis</td>
<td>Rodés-Cabau et al. (2011)84</td>
<td>Observational (29 transfemoral, 31 transapical)</td>
<td>Transapical or transfemoral</td>
<td>MRI</td>
<td>Transfemoral: 71 Transapical: 62</td>
<td>3</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Astarci et al. (2011)85</td>
<td>Observational (21 transfemoral, 14 transapical)</td>
<td>Transapical or transfemoral</td>
<td>MRI</td>
<td>Transfemoral: 90 Transapical: 93</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Ghanem et al. (2010)86</td>
<td>Observational (22)</td>
<td>Transfemoral</td>
<td>MRI</td>
<td>73</td>
<td>4</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Kahler et al. (2010)87</td>
<td>Case-control (31 TAVI, 21 surgical valve replacement)</td>
<td>Transfemoral</td>
<td>TAVI: 84 Surgical replacement: 48</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>Arnold et al. (2010)88</td>
<td>Observational (25)</td>
<td>Transapical</td>
<td>MRI</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td><strong>CABG surgery</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>CAD</td>
<td>Ito et al. (2012)89</td>
<td>Observational (449)</td>
<td>NA</td>
<td>MRI</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>CAD</td>
<td>Knopp et al. (2008)90</td>
<td>Observational (39)</td>
<td>NA</td>
<td>MRI</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>CAD</td>
<td>Gerrets et al. (2008)91</td>
<td>Observational (106)</td>
<td>NA</td>
<td>MRI</td>
<td>15 (in MRI cohort, n=86)</td>
<td>NA</td>
</tr>
<tr>
<td>CAD</td>
<td>Bendzus et al. (2002)92</td>
<td>Observational (35)</td>
<td>NA</td>
<td>MRI</td>
<td>26</td>
<td>0</td>
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<td><strong>Pulmonary vein isolation</strong></td>
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<tr>
<td>AF</td>
<td>Hauesler et al. (2013)93</td>
<td>Observational (37)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>AF</td>
<td>Neumann et al. (2011)94</td>
<td>Prospective pilot study (45 cryoballoon ablation, 44 radiofrequency energy technique)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>AF</td>
<td>Herrera-Skoldy et al. (2011)95</td>
<td>Observational (27 irrigated radiofrequency energy, 23 cryoballoon, 24 multielectrode phased radiofrequency)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>Irrigated radiofrequency energy: 7 Cryoballoon: 4</td>
<td>0</td>
</tr>
<tr>
<td>AF</td>
<td>Schwarz et al. (2010)96</td>
<td>Case-control (23 AF, 23 controls)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>AF</td>
<td>Gaita et al. (2010)97</td>
<td>Observational (232)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>14</td>
<td>0.4</td>
</tr>
<tr>
<td>AF</td>
<td>Schriechel et al. (2010)98</td>
<td>Observational (53)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>11</td>
<td>0</td>
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<td><strong>PFO closure</strong></td>
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<td>Patients with PFO and history of cryptogenic stroke</td>
<td>Skowasch et al. (2010)99</td>
<td>Observational (63)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>3</td>
<td>2</td>
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<tr>
<td>PFO</td>
<td>Dorenbos et al. (2007)100</td>
<td>Observational (35)</td>
<td>Trans-septal</td>
<td>MRI</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

*Of 39 patients who completed the imaging protocol

AF, atrial fibrillation; Ao, aortic; CAD, coronary artery disease; DWI, diffusion-weighted MRI; MDCT, multidetector computed tomography; NA, not available; PFO, patent foramen ovale; PCI, primary percutaneous coronary intervention; PVAC, pulmonary vein ablation catheter; PVI, pulmonary vein isolation; RCT, randomized controlled trial; SCIs, silent cerebral infarcts; TAVI, transcatheter aortic valve implantation.
Left cardiac catheterization

Coronary angiography and percutaneous coronary intervention (PCI) are standard invasive procedures in patients with ischaemic coronary artery disease. Ischaemic stroke has been described as an infrequent complication of these interventions, with incidences varying from 0.2% to 0.4% for cardiac catheterizations and 0.07% to 0.4% for PCI procedures. The frequency of SCIs in patients who have undergone such procedures has been shown higher than for ischaemic stroke, ranging from 2% to 35% (Table 2).

Numerous studies with periprocedural TCD monitoring have shown that catheterization causes gaseous as well as solid cerebral microemboli. Importantly, patients with SCIs were reported to have a considerably higher number of periprocedural solid microemboli compared with patients without SCIs, as measured using MRI. Blood clots formed on the tip of the catheter must be considered as a possible origin of cerebral emboli. Furthermore, solid microemboli can result from catheter manipulation in the aortic root, causing the release of small pieces of atherosclerotic debris. This mechanism is of particular relevance in the setting of extensive atheroma, which is an important consideration in patients undergoing cardiac catheterization who usually have generalized atherosclerosis. In a study of 1,000 patients undergoing PCI, 24–65% (depending upon the shape of the catheter used) had aortic atheromatous material retrieved from blood aspirated via the catheter. However, no association was found between the presence of this material and the in-hospital ischaemic complications, which might partially be explained by the sufficient withdrawal of blood containing the debris before injection of contrast. In this study, no routine neuroimaging was performed before or after procedure and, consequently, the potential relationship between atheromatous debris retrieved from the catheter and small thromboemboli resulting in SCIs could not be determined. Indeed, reported in-hospital ischaemic complications might be only the tip of the iceberg of procedural-related thromboemboli.

Total duration of the procedure and procedural fluoroscopy time have also been described as independent predictors of the occurrence of cerebral infarctions in patients undergoing angiography or PCI. Additionally, the frequency of postprocedural SCIs seems to vary according to the catheterization procedure used. In particular, retrograde catheterization of severe aortic valve stenosis is associated with a high rate of SCIs (22%). In patients undergoing retrograde catheterization of severe aortic valve stenosis, patient height (OR 8.24, 95% CI 2.71–25.02, \( P < 0.0001 \)) and a lower transvalvular gradient (OR 0.96, 95% CI 0.93–0.99, \( P = 0.027 \)) were associated with an increased risk of periprocedural SCIs. Furthermore, on the basis of previous observational data, the radial arterial access site for catheterization was associated with a higher increase of cerebral embolic complications than femoral arterial access. However, a 2012 multicentre, randomized trial, the SCIPION study, showed that the incidence of new SCIs after catheterization did not differ significantly between the femoral and radial arterial
approaches (11.7% versus 17.5%; OR 0.85, 95% CI 0.62–1.16, \( P = 0.31 \)) in patients with severe aortic stenosis scheduled for valve surgery. In addition to DWI, periprocedural TCD assessment of high-intensity transient signals was performed in a subgroup of patients and showed similar results for each access site.\(^{65} \) However, after completion, this study seemed to be underpowered. Therefore, although the arterial access site is unlikely to influence the frequency of SCIs after catheterization, large studies are required to confirm this finding. Such research is of particular importance given that coronary angiography is increasingly performed via the radial arterial access route.

**Transcatheter aortic valve implantation**

TAVI is an alternative treatment for patients with severe symptomatic aortic stenosis considered to be at high risk conventional surgical valve replacement, mostly elderly individuals with a high prevalence of atherosclerotic disease. Estimates of the risk of postprocedural stroke associated with TAVI vary from 1.5% to 10%.\(^{74,75} \) Using MRI, SCIs have been observed even more frequently than stroke, with prevalence ranging from 62% to 93% (Table 2).\(^{76-82} \) Kahlert and colleagues compared the rate of SCIs detected using MRI in patients undergoing transfemoral TAVI with historical controls who underwent surgical aortic valve replacement.\(^{76} \) Postprocedural SCIs were significantly more frequent in patients who underwent TAVI than in control individuals (84% versus 48%; \( P = 0.011 \)).\(^{76} \) Nonetheless, stroke was reported in only one patient who had undergone surgical aortic valve replacement, which necessitates further study of the relationship between the increased frequency of SCIs after TAVI and neurological complications.

Cerebral microemboli that occur after TAVI are probably caused during device positioning and implantation in the stenotic aortic valve. TCD studies provide important insight into the mechanisms of cerebral emboli during these procedures and have shown that deployment of the valve prosthesis during TAVI is associated with the highest frequency of high-intensity transient signals.\(^{83-85} \) In addition, hypoperfusion after rapid right ventricular pacing during deployment of the valve prosthesis might also be related to ischaemic brain injury.\(^{86} \)

The two most-widely used approaches for TAVI are the transfemoral and transapical routes. During the more-commonly used transfemoral approach, a large catheter (18–24 F) containing the valve is advanced through the aortic arch and crossed retrograde over the severely diseased native aortic valve. The alternative transapical approach is preferred in patients with diseased or severely calcified iliofemoral arteries, and involves direct puncturing of the ventricular apex through a small left lateral thoracotomy. A catheter is then inserted through the ventricular apex in the mid portion of the ventricular cavity, through which the valve is advanced and placed in the native aortic valve. Given that manipulation of large catheters in the aorta and the retrograde crossing of the native aortic valve are avoided using the transapical procedure, this technique was
assumed to cause a lower rate of postprocedural SCIs than the transfemoral approach. However, in prospective multicentre study in which the incidence of SCIs in patients who underwent either transfemoral or transapical TAVI was compared, no significant difference was observed between the two approaches (66% and 71%, respectively; $P = 0.78$). Of the new cerebral microinfarcts identified using DWI, 91% were <1 cm, 76% were multiple in number, and 73% involved both cerebral hemispheres. Most lesions found on DWI were clinically silent, except in two patients, one from each treatment group, who experienced symptomatic cerebral emboli within 24 h of the procedure. In addition to DWI, cognitive function assessment was performed before and 6 days after the procedure, with no significant differences recorded between patients with or without new cerebral lesions. However, this result might be attributable to the short evaluation time or the lack of sensitivity of the cognitive assessment. Unfortunately, no long-term data are currently available on the incidence of SCIs or stroke after TAVI, and the possible effects on cognitive decline, and dementia.

**CABG surgery**

Interest in postprocedural cerebral complications, such as symptomatic cerebral infarcts, SCIs, and postoperative cognitive decline, after CABG surgery is increasing. Indeed, the occurrence of SCIs after cardiac surgery has been assessed in several studies, showing an incidence between 15% and 51% (Table 2).

Additionally, postoperative cognitive decline is a frequent cerebral complication after CABG surgery, detected in 14–48% of patients at postoperative follow-up. The clinical consequences of cognitive decline are numerous and result in increased use of healthcare resources.

The aetiology of postoperative cognitive decline is probably multifactorial. However, studies using TCD have detected showers of emboli periprocedurally during CABG surgery particularly during cannulation and clamping of the aorta. Furthermore, in patients undergoing CABG surgery, the extent of atheromatous disease of the ascending aorta and the aortic arch has been associated with the microembolic load during periprocedural TCD monitoring and on postprocedural DWI. Moreover, the occurrence of postprocedural SCIs is postulated to be higher after CABG surgery combined with aortic valve replacement than after CABG surgery alone.

Investigators in various studies have assessed whether SCIs detected using DWI are associated with cognitive dysfunction after CABG surgery. However, in most of these studies, cognitive function was assessed early postoperatively and variable results have been reported. A fairly small study ($n = 39$) with a 3-year follow-up period showed a two-stage course of cognition after CABG surgery: early cognitive decline during the initial days after surgery (until hospital discharge) that improved at 3 months, followed by a second cognitive decline observed at 3 years after surgery. In this study, SCIs
reported postoperatively using DWI were not associated with early or late cognitive decline.\textsuperscript{87}  
Off-pump CABG surgery without cardiopulmonary bypass and reduced aortic manipulation was assumed to result in fewer new SCIs than on-pump CABG surgery. However, a large randomized trial ($n = 281$) showed no significant difference in the frequency of cognitive dysfunction at 3-month or 12-month follow-up between on-pump and off-pump CABG surgery.\textsuperscript{99} Unfortunately, no MRI was performed to assess the occurrence of SCIs in the individuals enrolled in this study. The findings were supported by the study of Lund and colleagues, who observed no significant difference between off-pump and on-pump CABG surgery in the rate of new postoperative SCIs lesions and cognitive decline at 3 months after surgery.\textsuperscript{91}

**Pulmonary vein isolation**

International clinical guidelines have established PVI an important treatment strategy in patients with AF who remain symptomatic despite optimal medical therapy, and in patients in whom the potential benefit is sufficient to justify an ablation procedure.\textsuperscript{100} Various pulmonary vein ablation strategies, including segmental PVI and circumferential antral PVI with or without linear lesions, and techniques such as radiofrequency energy or cryoballoon technique, can be used. Thromboembolic complications after PVI in patients with AF have been described, typically occurring within the first 24 h after pulmonary vein ablation and with an increased risk in the first 2 weeks after the procedure. Various studies have shown that the incidence of SCIs after PVI is between 8% and 41%.\textsuperscript{29,101–105}

In the prospective pilot MEDAFI-TRIAL,\textsuperscript{29} the incidence of cerebral emboli detected using MRI was assessed in patients undergoing PVI with either the cryoballoon or the radiofrequency ablation technique. New SCIs were found in 7.9% of the patients within 1 day after pulmonary vein ablation (Table 2), with no significant differences between the two treatment modalities, and none of the patients developing symptomatic cerebral infarcts after procedure.\textsuperscript{29} Furthermore, the occurrence of SCIs and their relationship with postprocedural cognitive functioning were assessed in patients with symptomatic paroxysmal AF undergoing left atrial catheter ablation in the MACPAF study.\textsuperscript{101} New postprocedural MRI-detected SCIs were reported in 41% of the patients, although these ischaemic lesions were not associated with cognitive impairment immediately after the procedure or at 6–9 month follow-up.\textsuperscript{101}

**Patent foramen ovale closure**

Currently, whether patients who experience a cryptogenic stroke and have a PFO should be treated with closure of the PFO, or whether medical therapy with anticoagulants is sufficient for secondary prevention of ischaemic events, is heavily debated. Intention-to-treat analyses have not revealed a substantially reduced rate of recurrent stroke, TIA, or
death in patients treated with PFO closure compared with medical therapy alone.\textsuperscript{106,107} However, Meier and colleagues noted that, after completion, their study seemed to be underpowered, making it difficult to detect a clinical benefit of PFO closure.\textsuperscript{106} Observational studies have shown a 3\%\textsuperscript{108} and 6\%\textsuperscript{109} incidence of SCIs after PFO closure in patients who had suffered from a cryptogenic stroke (Table 2). Nevertheless, the relationships between PFO closure, SCIs, and neurological complications remain unclear and should be the subject of future studies.

\textbf{CLINICAL IMPLICATIONS OF SCI LESIONS}

Improvements in anticoagulation therapy and invasive cardiac interventions have led to a decrease in the prevalence of cardioembolic stroke. Despite these improvements, advancements in neuroimaging have resulted in an increased awareness of subclinical SCIs, which are much more prevalent than symptomatic stroke. SCIs detected in daily clinical practice are often found by chance, as a consequence of neuroimaging performed to address some other clinical question. Owing to the lack of symptoms associated with SCIs, these incidental findings are frequently disregarded. However, whether these lesions are ‘innocent’ bystanders or contributors to neurological conditions remains unclear.

Large observational population-based studies, such as the Rotterdam Scan\textsuperscript{17} and the Cardiovascular Health Study,\textsuperscript{110} were among the first investigations of the occurrence of SCIs and their association with the risk of future stroke, cognitive decline, and dementia. In the Cardiovascular Health study,\textsuperscript{110} participants with SCIs detected using MRI had an increased incidence of stroke during the 4-year follow-up period compared with individuals without SCI lesions (18.7 versus 9.5 per 1,000 persons per year). Furthermore, the adjusted relative risk of stroke increased in individuals with multiple SCIs (HR 1.9, 95\% CI 1.2–2.8).\textsuperscript{110} In the Rotterdam Scan Study,\textsuperscript{17} the presence of SCIs increased the risk of stroke more than threefold, independently of other risk factors (adjusted HR 3.9, 95\% CI 2.3–6.8). The increased risk of stroke associated with SCIs might be attributable to the underlying conditions, such as cardiac disease, that also caused the SCIs and are conceivably still influencing the patient. However, in the setting of SCIs caused by an external event, such as invasive cardiac intervention, whether the procedure is associated with the risk of subsequent stroke beyond the initial postprocedure period remains unclear and warrants future study.

In addition to their association with an increased risk of stroke, MRI-detected SCIs have been reported to more than double the risk of dementia and, in particular, Alzheimer disease in the general population.\textsuperscript{13} Furthermore, MRI studies in patients with vascular dementia have supported the concept that the cumulative burden of ischaemic brain injury resulting from multiple SCIs contributes to cognitive decline.\textsuperscript{110,111} Interestingly,
the decline in different cognitive domains has been found to be associated with the location of SCIs detected using MRI. Although the pathophysiological mechanism underlying dementia is likely to be heterogeneous, various mechanisms can be postulated to explain the observed association between SCIs and Alzheimer disease. For example, SCIs occurring in a brain already affected by Alzheimer disease might further impair cognition, resulting in the final diagnosis of dementia. However, such lesions might also trigger the development of neurofibrillary tangles and senile plaques, which potentiates the abnormalities associated with Alzheimer disease.112

Several studies have also shown that major depression occurring for the first time during or after the presenile period might be related to SCIs, an event that might be comparable to depression after a stroke.113–116 When the clinical outcome in patients with depression aged >50 years was investigated over a 3-year period, MRI-detected SCIs were found to be associated with an increased frequency and longer duration of hospital admission owing to depression.115 Furthermore, Fujikawa and colleagues found that SCIs identified using MRI were more frequently observed in senile (individuals aged >65 years) depression than in presenile (individuals aged 50–60 years) depression (93.7% versus 65.9%; \( P < 0.01 \)).114

Importantly, the increases in the risk of future stroke, cognitive decline, dementia, and depression associated with SCI lesions discussed above were not observed in the setting of cardiac disease or interventional cardiology procedures. Nonetheless, these results support the potential clinical influence of SCIs. Moreover, AF has been independently associated with an increased risk of dementia,36 and SCIs might represent the underlying mechanism; however, this possibility needs to be further investigated. Additionally, several studies have investigated the relationship between SCIs and cognitive decline after invasive cardiac interventions, such as TAVI, CABG surgery, and PVI, and PFO closure. These studies had different follow-up time and reported contradictory results, which complicates comparison between studies. Therefore, future studies are required to clarify the associations between cardiac procedures, SCIs, and neurological conditions.

Whether SCIs are truly asymptomatic is still a subject of debate. Evidently, whether a cerebral infarct detected on neuroimaging is ‘silent’ depends on the vantage point of both the patient and physician and might even differ between the two (Figure 2). Some patients might not be aware that the symptoms they experienced were caused by a cerebral infarct, or clinical evaluations might not have been performed at the time, so a stroke was never diagnosed. Several studies have used other terms for ‘silent’ such as ‘prior’, ‘covert’, or ‘subclinical’ cerebral microinfarcts. Indeed, the variation in terms and definitions of SCIs used among the studies performed to date limits cross-study comparisons, which are important for interpretation of the pathological correlation and clinical consequences of such lesions. Therefore, future studies should describe the criteria used to defined ‘silent’ infarcts, as well as the types of neurological examinations performed.
CONCLUSIONS

The occurrence of SCIs in cardiac disease and after invasive cardiac procedures is frequently observed. AF\textsuperscript{26-32} and cardiomyopathy\textsuperscript{41,44} have been associated with an increased occurrence of SCIs. Other cardiac diseases likely to be related to an increased incidence of SCIs, but which require further investigation, are LV thrombus formation and PFO. Furthermore, the development of new SCI lesions after cardiac interventions is gaining increasing research interest. Left heart catheterization,\textsuperscript{66} TAVI,\textsuperscript{76} CABG surgery,\textsuperscript{87} and PVI\textsuperscript{101} have all been linked with a high frequency of SCIs, with TAVI having the highest incidence of postprocedural SCIs (62-84% of patients).\textsuperscript{76-82} Although PFO closure in relation to stroke has been extensively investigated, the occurrence of SCIs after this intervention has not been widely studied.

Additionally, various large, population-based studies have shown that SCIs double the risk of future stroke and can be considered a prodromal symptom before the development of clinical stroke. Moreover, increasing evidence suggests that these ‘silent’ cerebral lesions are associated with an increased risk of cognitive impairment, subsequent dementia, and depression. Therefore, detection of SCIs might facilitate the management
of patients with cardiac disease and those undergoing invasive cardiac interventions. Given the high incidence of SCIs in cardiac diseases and after interventional cardiology procedures used to treat them, further research assessing the prognostic implications of these lesions, as well as their possible prevention or management, are warranted.

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REVIEW CRITERIA
REFERENCES

Silent cerebral infarcts in relation to cardiac disease and procedures


