

# Atrial fibrillation and silent stroke: links, risks, and challenges

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**Abstract:** Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a projected number of 1 million affected subjects in Germany. Changes in age structure of the Western population allow for the assumption that the number of concerned people is going to be doubled, maybe tripled, by the year 2050. Large epidemiological investigations showed that AF leads to a significant increase in mortality and morbidity. Approximately one-third of all strokes are caused by AF and, due to thromboembolic cause, these strokes are often more severe than those caused by other etiologies. Silent brain infarction is defined as the presence of cerebral infarction in the absence of corresponding clinical symptomatology. Progress in imaging technology simplifies diagnostic procedures of these lesions and leads to a large amount of diagnosed lesions, but there is still no final conclusion about frequency, risk factors, and clinical relevance of these infarctions. The prevalence of silent strokes in patients with AF is higher compared to patients without AF, and several studies reported high incidence rates of silent strokes after AF ablation procedures. While treatment strategies to prevent clinically apparent strokes in patients with AF are well investigated, the role of anticoagulatory treatment for prevention of silent infarctions is unclear. This paper summarizes developments in diagnosis of silent brain infarction and its context to AF.

**Keywords:** atrial fibrillation, silent strokes, cardiac embolic events, stroke risk

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting an estimated 1% of the population.<sup>1</sup> Its prevalence increases age dependently, from <0.1% in adults younger than 55 years to 8% in persons aged 80 years or older.<sup>1</sup> Approximately every fourth person over 40 years will suffer from AF in his or her life.<sup>2</sup> Changes in the age structure of Western populations lead to the assumption that the number of affected patients will at least duplicate by the year 2050.<sup>1</sup> Large trials and epidemiological investigations showed a doubled increase in mortality in AF patients,<sup>3,4</sup> including patients with “silent AF”.<sup>5</sup> Approximately one-third of all strokes are caused by AF, and AF-caused strokes are often more severe than non-AF-related strokes.<sup>6–9</sup> Data from the Framingham Study showed a three- to five fold increased risk of stroke in AF patients.<sup>10,11</sup> AF often occurs with no or only few symptoms and is therefore often undiagnosed or only diagnosed when complications like stroke or heart failure occur.<sup>5,12</sup> On the other hand, many studies reported a significantly higher percentage of silent strokes in AF patients diagnosed by different methods of cerebral imaging compared to patients without AF history.<sup>13–16</sup> Effective oral anticoagulation (OAC) therapy can decrease the rate of stroke up to 80% in AF.<sup>17</sup>

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Silent cerebral infarction (SCI) is defined as the presence of cerebral infarction in the absence of corresponding clinical symptomatology. SCI is a part of cerebral small-vessel disease, which includes white matter hyperintensities and cerebral microbleeds.<sup>18</sup> Progress in imaging technology simplifies diagnostic procedures of these lesions. There is still no final conclusion about frequency, risk factors, and clinical relevance of these lesions.

AF patients with silent and hitherto undiagnosed stroke are often not treated with oral anticoagulants, and the impact of this therapy on SCIs remains unclear and needs further investigation.<sup>19</sup>

## Silent stroke and silent cerebral lesions

### Prevalence and incidence of silent strokes in common populations

In 1965 Fisher<sup>20</sup> first described cerebral infarction without any clinic symptoms. Studies of the past years showed that these lesions are not as benign as originally thought.<sup>21</sup> In long-term analyses, these lesions correlate with neurological and cognitive deficits and psychiatric disorders in elderly patients.<sup>21</sup> Silent cerebral ischemia is now recognized as part of a spectrum of cerebrovascular disease, which also includes transient ischemic attack (TIA) and stroke.<sup>18</sup> A change in terminology to “covert infarction” is in discussion.<sup>22</sup>

Depending on the definition of stroke, prevalence of SCI can range. A prevalence of 10.7% was mentioned in the Framingham Offspring study.<sup>23</sup> In this study, stroke was defined by clinical symptoms for more than 24 hours. Most remaining published community sample studies showed a prevalence between 10% and 20%. In Routine Health Care Studies, an SCI range between 5% and 62% has been reported.<sup>21</sup> Incidence data are rare. Rates from 1.9% to 3.7% per year are reported, with patients age being an important risk factor for SCI.<sup>21</sup> Uehara et al<sup>24</sup> showed that 8% of the 60–69-year old participants had new lesions over the duration of follow-up and that 22% of those patients were older than 80 years. The Rotterdam Scan Study examined 1,077 patients without clinical symptoms or history of stroke. Statistical analyses showed an increased risk of 8% per year for an SBI after reaching the age of 60 years.<sup>25</sup> In conclusion, SCIs are approximately ten times more frequent than a stroke.<sup>26</sup>

### Diagnosis of SCI

Most studies use diffusion-weighted magnetic resonance imaging (DW-MRI). Data show a significantly higher sensitivity to detect lesions than computed tomography (CT).<sup>27,28</sup>

Information from earlier studies using autopsy is unclear because of the limited sensitivity to detect small lesions due to thick slices and large interslice gaps.<sup>29</sup>

Cerebral ischemia can be detected within minutes after onset by detection of a hyperintense lesion on DWI indicating cellular edema and hypointense presentation in apparent diffusion coefficient (ADC) map. In contrast to ADC map detection, the T2-weighted fluid-attenuated inverse recovery sequence (FLAIR) turns positive in delay.<sup>30</sup> To distinguish silent brain infarction from dilated Virchow–Robin spaces and leukoaraiosis, additional criteria include a lesion size of 3 mm or greater and presence of a hyperintense rim around the hypointense lesion on FLAIR images.<sup>29,31</sup>

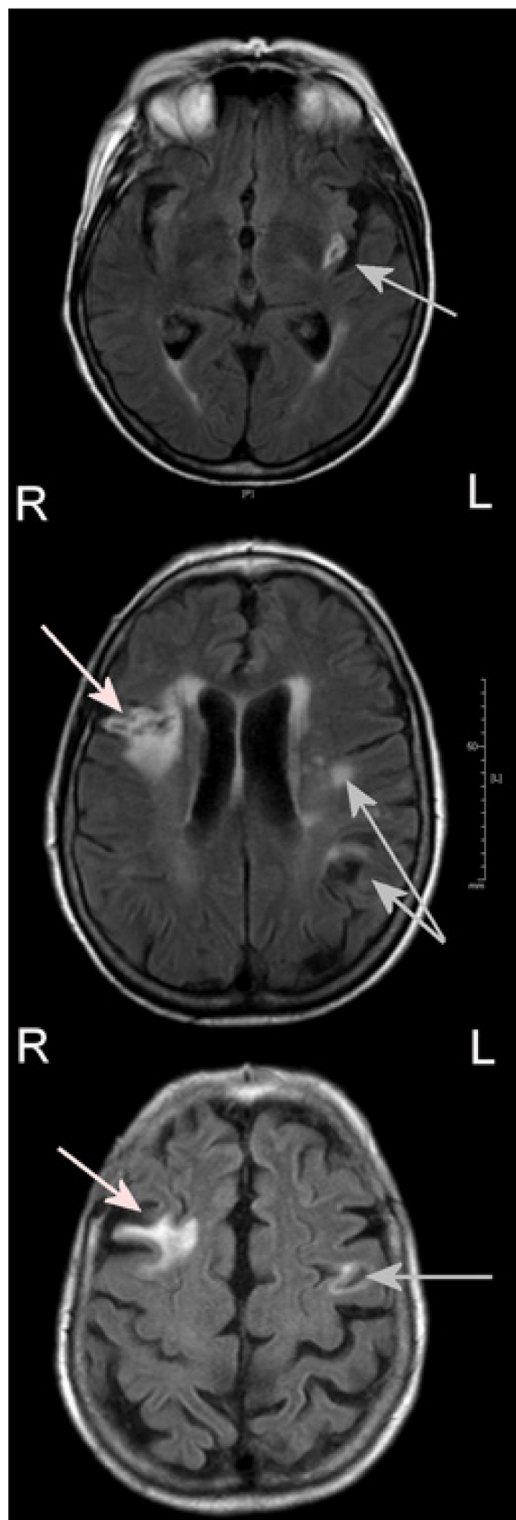
Further improvement in imaging modalities gives the possibility of further subclassification of silent brain infarction. A silent cerebral event (SCE) is defined as an acute new hyperintense DWI-lesion with reduced ADC.<sup>30</sup> Recent publications renounce FLAIR positivity because of delayed detection and reduced sensitivity for early diagnosis of SCI.<sup>32</sup> FLAIR-positive MRI lesions were differentiated as silent cerebral lesions (SCLs; Figures 1 and 2). The best time point for brain MRI evaluation of SCI in asymptomatic patients is still unclear.<sup>30</sup>

Most silent infarctions are localized in the subcortex.<sup>33</sup> Only 10% of infarctions are localized in the cortex.<sup>26</sup> Location of infarction could at least partly explain symptomatic versus covert lesions, because infarction in the internal capsule is associated with a higher probability of symptoms compared to those in other brain regions. Sizes of lacunas were not related to symptoms in studies.<sup>20,34</sup> Valdés-Hernández et al<sup>34</sup> showed that the number of silent infarctions correlates with the risk of clinical stroke.<sup>34</sup>

### Risk factors for SCI

Data about risk factors are obtained from community-based samples. Risk factors with a strong association with SCI are age, hypertension, metabolic syndrome, carotid artery disease, and chronic kidney disease.<sup>21,35</sup> The most clear risk factor is age. A meta-analysis by Fanning et al<sup>21</sup> showed an OR of prevalent SCI assessed per year of age ranging from 1.03 (95% CI: 0.98, 1.08) to 1.13 (95% CI: 1.09, 1.18) and per decade ranging from 2.44 (95% CI: 1.84, 3.23) to 3.21 (95% CI: 2.17, 4.74). Hypertension resulted in a microangiopathy of several organ systems. Chronic kidney disease and cerebral microangiopathy with lacunar infarction is the final common pathway of hypertension.<sup>18</sup>

Other demographic characteristics and their risk for SCI are still in discussion: The Rotterdam Scan Study and the Cardiovascular Health Study identified a 30%–40% increased



**Figure 1** MRI (FLAIR-weighted sequence) of a 76-year-old patient with chronic atrial fibrillation.

**Notes:** Approximately 3 years ago, cortical stroke on the right side (white arrow). Silent brain infarction on the left side without clinical symptoms (gray arrow). With kind permission from Springer Science + Business Media: *Nervenarzt*, Silent brain infarctions, Volume 82(8), 2011, pages 1043–1052, Ritter MA, Dittrich R, Ringelstein EB. © Springer-Verlag 2011.<sup>103</sup>

**Abbreviations:** FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.



**Figure 2** MRI of a 61-year-old patient with embolic silent brain infarction in cerebellum (arrow).

**Note:** With kind permission from Springer Science + Business Media: *Nervenarzt*, Silent brain infarctions, Volume 82(8), 2011, pages 1043–1052, Ritter MA, Dittrich R, Ringelstein EB. © Springer-Verlag 2011.<sup>103</sup>

**Abbreviation:** MRI, magnetic resonance imaging.

prevalence in females.<sup>36,37</sup> Fukuda et al<sup>38</sup> showed a fourfold increased risk for SCI in early menopausal women. The majority of studies do not support any disparity between the sexes, so the effects of this factor remain unclear.<sup>21</sup>

A low alcohol consumption is associated with a reduced risk of stroke morbidity and mortality.<sup>39</sup> Lee et al<sup>40</sup> (one or two times a week) and Mukamal et al<sup>41</sup> (one to six standard drinks per week) showed a protective effect for mild consumption. However, data are inconsistent. Data from Japan showed an increased risk of SCI associated with alcohol consumption, so perhaps ethnic differences in alcohol metabolism may play a role in the risk profile.<sup>21,42</sup>

There are only few studies showing a statistically significant association between smoking and SCI. Howard et al<sup>43</sup> showed in 1998 a relationship between exposure to cigarette smoke and SCI, in accordance to the higher incidence of carotid atherosclerosis. In a cohort of 432 females, an association between “natural” early menopause and SCI was shown. Cigarette smoking, malnutrition, and lower socioeconomic status have been associated with earlier menopause.<sup>38</sup>

Larger studies like the Rotterdam Study showed an association between the presence of diabetes mellitus and pack-years of smoking with symptomatic, but not with silent, infarcts.<sup>44</sup> In conclusion, the relevance of smoking remains unclear actually.

Abdominal obesity seems to be a risk factor for SBI too. Park et al<sup>45</sup> showed an increased risk for SCI for patients

with a waist circumference  $\geq 102$  cm (male) or  $\geq 88$  cm (female). Studies analyzing body mass index data showed conflicting results. In a study by Bokura et al,<sup>46</sup> a body mass index  $\geq 25$  kg/m<sup>2</sup> was accompanied with a higher risk for SCI. This study only included patients with a metabolic syndrome. Other studies could not confirm these results.<sup>21,47</sup> In conclusion, an abdominal obesity in the context of a metabolic syndrome seems to be a more important risk factor than other forms of obesity.

## SCIs – not so silent?

SCI can be seen as a part of cerebrovascular disease with a long-term worsening in brain function. Liebetrau et al<sup>48</sup> showed, in 2004, that almost one-fifth of 239 85-year-old participants have infarctions on CT, half of them had no clinical symptoms. These infarctions were related to an increased rate of dementia and 3-year mortality. Data from other large studies confirm these findings.<sup>36,49,50</sup>

Patients recognizing stroke symptoms are a prerequisite to differentiate between SCI and TIA or stroke. A study of Howard et al<sup>51</sup> in 2006 including 18,462 participants without stroke anamnesis showed that 17.8% had in history one or more stroke symptoms after exact neurological anamnesis. Ethnic group, income, and educational level can influence detection of physical symptoms.<sup>51</sup> Furthermore, patients exclude symptoms, for example, for fear of severely diseases. Ritter et al<sup>26</sup> showed in their study that theoretical knowledge of symptoms and action knowledge were not found to be significantly associated with shorter prehospital times.

Data from Song et al<sup>52</sup> presented an increased severity of cognitive decline in patients with Alzheimer's disease and SCI compared to patients with Alzheimer's disease.<sup>52</sup>

Yamashita et al<sup>53</sup> demonstrated in a long-term follow-up study that the presence of SCI was associated with a poor prognosis in geriatric depression compared with depressive patients without infarction. Similar to these findings, Fujikawa et al<sup>54</sup> showed that for late-onset mania beginning after age of 50, the incidence of SCI was significantly higher than that of patients with early-onset affective disorders ( $P < 0.05$ ).

Several studies showed an increased risk of stroke after detecting SCI or subcortical white matter lesions.<sup>55–57</sup> To avoid stroke with severe functional impairment, an improved diagnosis with optimized scoring systems and optimized prevention treatment is necessary.<sup>22,58</sup>

## SCI in AF

AF was identified as an independent predictor of SCI in a large autopsy study in Japan.<sup>33</sup> During the last decades, a couple of studies investigated the relationship between AF

and the occurrence of SCI diagnosed by different methods of brain imaging. A large number of patients were evaluated using cranial CT. More than 2,000 probands were enrolled in diagnostic studies; SCI rates between 15% and 50% in AF patients were observed,<sup>15,59–61</sup> and a stroke rate of 7% during a follow-up period of 3 years in AF patients has been reported.<sup>59</sup> In collectives without a history of stroke and TIA, SCI prevalence was lower compared to collectives without exclusion of these high-risk patients. It seems that the influence of AF duration is not of clinical relevance; the prevalence between paroxysmal and chronic AF patients did not significantly vary.<sup>61</sup> Petersen et al were not able to show a higher SCI rate in patients with AF compared to patients without AF, but they found a significantly higher prevalence of regions with white matter tissue loss in AF patients compared to patients without AF.<sup>61</sup> Raiha et al<sup>14</sup> investigated the relationship between vascular factors and white matter low attenuation (WMLA) of the brain in CT and found a prevalence of WMLA of 73% in a small subgroup of 30 patients with AF compared to 48% in non-AF patients. In recent years, several studies investigated the relationship between SCI diagnosed by MRI and AF: The Framingham Offspring Study showed an increased risk of midlife SCI in patients with AF (OR 2.16) by MRI scan.<sup>23</sup> In dependence of different scan techniques and sequences and their specific image resolution, SCI rates in AF patients between 12.3% and 92% have been reported compared to rates between 17% and 69% in non-AF patients.<sup>16,62–64</sup> Gaita et al<sup>13</sup> found an SCI rate of 92% in patients with persistent AF, a rate of 89% in patients with paroxysmal AF, and a rate of 46% in patients without AF, and thus was also not able to show a relationship between SCI prevalence and AF duration.<sup>13</sup> In a subgroup of patients with type 2 diabetes mellitus, SCI rates of 61% in patients with silent AF were reported compared to 29% in patients without silent AF ( $P < 0.01$ ).<sup>62,65</sup> Thus, the prevalence of SCI in AF patients is higher than in controls, albeit the prevalence varies widely between the different studies. The prevalence seems to be dependent on the sensitivity of the diagnostic tool and the comorbidities of the investigated collective. Table 1 summarizes sample sizes and event rates of the different studies.

## Silent stroke and aortic or AF-related left atrial appendage abnormalities

The relationship between AF and SCI is not completely understood. Kobayashi et al<sup>63</sup> assumed a synergistic effect of microthrombi and hemodynamic abnormalities. In patients with AF, risk factors for clinically symptomatic thromboembolism have been identified: The SPAF III study identified left

**Table I** Summary of SCI studies in patients with AF

Diagnostic tool	Year	Study	Participants	Study design	SCIs	P-value AF vs non-AF
Autopsy	1995	Shinkawa et al <sup>33</sup>	966 (AF% unknown)	Nonstroke vs silent stroke vs stroke	125 (12.9%)	$P<0.05$ (nonstroke vs silent stroke)
CT	1987	Petersen et al <sup>61</sup>	58 (50% AF)	Patients with AF > 1 year vs patients with no AF history	14 (48%) in AF vs 8 (28%) in non-AF	$P>0.1$
	1988	Kempster et al <sup>15</sup>	222 (24% AF)	Patients with AF > 1 year vs patients without AF	7 (13%) in AF vs 7 (4%) in non-AF	$P<0.05$
	1993	Raiha et al <sup>14</sup>	204 (15% AF)	Records with CT scans from one hospital	73% in AF vs 48% in non-AF	$P=0.00959$
	1995	Ezekowitz et al <sup>59</sup>	516 (100% AF)	Patients with nonrheumatic AF	14.7% at baseline Between 1.01% and 1.57% during FU	–
	1996	EAFT Study Group <sup>60</sup>	985 (100% AF)	Patients with nonrheumatic AF and history of TIA or nondisabling ischemic stroke	14%	–
MRI	2008	Das et al <sup>23</sup>	2,040 (2.2% AF)	Longitudinal community-based study	220 with SCI (5% AF) 1,820 without SCI (1.9% AF) (HR 2.16)	$P=0.033$
	2011	Neumann et al <sup>82</sup>	89 (100% AF)	Single-center study	12.3%	–
	2012	Kobayashi et al <sup>63</sup>	142 (50% AF)	Patients with nonvalvular AF vs controls without AF	74.6% in AF 57.7% in non-AF	$P=0.03$
	2013	Gaita et al <sup>13</sup>	270 (180 with AF, 50% paroxysmal, 50% persistent AF)	Patients with paroxysmal AF vs persistent AF vs controls	89% in paroxysmal AF vs 92% in persistent AF vs 46% in controls	$P=0.59^*$ $P<0.01^{**}$
	2013	Stefansdottir et al <sup>16</sup>	4,251 (330 with AF [8%])	Longitudinal study	48.8% in AF vs 28.6% in non-AF	$P<0.001$
	2013	Marfella et al <sup>65</sup>	464 (38% AF)	Longitudinal observational study, FU over 37 months for stroke events	Baseline SCI 61% in AF vs 29% in non-AF stroke events during FU 17.3% in AF vs 5.9% in non-AF	$P<0.01^{***}$ $P<0.01^+$
	2014	Chen et al <sup>64</sup>	935 (48 with AF)	Prospective cohort study	33.3% in AF vs 17.3% in non-AF	?

**Notes:** \*P-value paroxysmal vs persistent AF. \*\*P-values paroxysmal AF vs controls and persistent AF vs controls. \*\*\*Baseline P-value AF vs non-AF. +FU P-value AF vs non-AF.

**Abbreviations:** AF, atrial fibrillation; CT, computed tomography; FU, follow-up; MRI, magnetic resonance imaging; SCI, silent cerebral infarction; vs, versus; TIA, transient ischemic attack; HR, hazard ratio.

atrial abnormalities like a left atrial thrombus, spontaneous echo contrast (SEC), or an abnormal left atrial appendage (LAA) emptying velocity<sup>66</sup> and also aortic abnormalities like large ( $\geq 4$  mm), ulcerated, or mobile plaques as risk factors for clinically symptomatic thromboembolisms, all investigated by transesophageal echocardiography (TEE).<sup>66</sup> However, the mechanisms leading to SCI in patients with nonvalvular AF are not well investigated. Very recently, one study investigated the role of left atrial or aortic abnormalities diagnosed by TEE in silent stroke: Sugioka et al<sup>67</sup> identified a higher prevalence of SCI in patients with left atrial abnormalities compared to patients without left atrial abnormalities (58% vs 22%;  $P<0.001$ ) and in patients with complex arch plaques compared to patients without arch plaques (74% vs 20%;  $P<0.001$ ). Left atrial abnormalities and complex arch plaques were independent risk factors of SBI.<sup>67</sup> Thus, abnormalities in the left atrium and complex arch plaques

could play an important role in the occurrence of SCI. The authors only found a low prevalence of left atrial thrombus formation, but much higher rates of SEC or abnormal low emptying velocities in the LAA.<sup>67</sup> Some studies identified SEC as a risk factor of thromboembolism.<sup>66,68,69</sup> Possible mechanisms are an SEC-related fibrinogen-mediated erythrocyte aggregation<sup>70</sup> and microembolization of small thrombi arising in the fibrillating LAA.<sup>13,71</sup>

## SCI related to AF ablation procedures

Pulmonary vein isolation (PVI) has become a standard therapeutic strategy in the treatment of symptomatic AF.<sup>72</sup> Complication rates of 3%–5% have been reported, with procedure-associated stroke being one of the most severe complications occurring in less than 1%.<sup>73</sup> A large survey of more than 1,000 procedures reported an occurrence of acute stroke in 0.6%.<sup>74</sup> The incidence of SCI varies widely more or less

dependent of the ablation technology. Within the framework of studies, postablation MRI was performed in more than 1,700 patients and SCI/SCL rates of 12.6% were derived, with an estimated incidence of 9.3% after irrigated radiofrequency (IRF) ablation and of 20.9% using phased duty-cycled radiofrequency pulmonary vein ablation catheter (PVAC).<sup>30</sup> The largest group of SCL or SCE investigations were patients after IRF pulmonary vein ablation with rates between 7.4% and 24%;<sup>75–77</sup> the incidence of FLAIR-independent SCE was reported between 6.8% and 24%,<sup>78–84</sup> with lower incidence in patients under continued OAC.<sup>81,82</sup> Table 2 summarizes the incidence rates and study details.

The number of investigated patients after PVAC procedure is quite smaller. In 2011, three independent studies reported incidence rates of SCE/SCL > 35%.<sup>75,77,79</sup> Modifications in ablation procedure led to a significant reduction in SCE/SCL, with lowest rates in the ERACE trial (Table 2).<sup>32,85,86</sup> They revealed an incidence of only 1.7%, which is the lowest incidence rate of any ablation technology so far by three specific procedural changes: 1) the procedure was performed under heparin application (activated clotting time (ACT) > 350 ms) and under continued OAC; 2) they minimized air ingress; and 3) they deactivated the distal or proximal electrode to avoid radiofrequency interaction.<sup>86</sup>

The number of investigated patients after cryoballoon ablation is the smallest one compared to the previously reported ablation techniques, with an incidence of SCL/SCE of 14.5%.<sup>30</sup> SCL incidence rates were lowest after cryoballoon ablation, followed by IRF ablation and highest after PVAC ablation.<sup>13,75</sup> Thus, all actually used ablation techniques of AF lead to an periprocedural occurrence of new SCI, but the clinical relevance of these lesions is unclear and not well investigated. Table 2 summarizes the results of published studies.

The intraprocedural application of heparin to avoid thromboembolic complications monitored by measurements of ACT is recommended. One study identified ACT values > 320 seconds as the only independent predictor of SCLs, an ACT increase of one point led to a reduction of stroke risk of 0.4%.<sup>87</sup> Another study reported a threefold increase in SCLs if only one ACT value of < 300 seconds was measured.<sup>76</sup> They also identified the waiving of heparin bolus before transseptal punctation as risk factor for SCL.<sup>88</sup> In contrast to this finding, a second study reported no influence of mean or minimal ACT on occurrence of SCI under continued intake of OAC.<sup>81</sup>

A stable antithrombotic milieu during the ablation procedure is useful to avoid complication. Several studies reported lower periprocedural complication rates if OAC was

continued.<sup>89–91</sup> A couple of studies showed that continuation of OAC leads to lower SCL rates: Gaita et al<sup>92</sup> reported a more than threefold increased risk of SCL if INR values below 2.0 were measured. Comparable results were reported on continuation of rivaroxaban intake without an increase of bleeding complications.<sup>93</sup> In contrast to these findings, Martinek et al<sup>81</sup> concluded that continuation of OAC is not able to prevent cerebral embolism. Data of other direct oral anticoagulants (DOAC) are sparse, but similar results as reported for rivaroxaban are hypothesized.

In fact, no periprocedural monitoring system for SCI exists; a few studies tried to detect periprocedural microembolic events by continuous registration of transcranial Doppler (TCD) signals, but a relationship between occurrence of periprocedural microembolic events in TCD and the detection of SCI in MRI after the procedure has not been reported yet.<sup>30,94</sup> Kochhäuser et al<sup>95</sup> reported a significantly increased number of periprocedural microembolic events during PVI using PVAC compared to IRF procedure, but they were not able to detect any differences in neuropsychological assessment between the different ablation techniques, and they only found a subtle, diffuse postprocedural impairment of neuropsychological function depending on age and the number of detected microembolic events. Thus, the role of microembolic events as a potential cause of SCI remains unclear and actually not well investigated.

There is low evidence that waiving or postponing of periprocedural electrical cardioversion may decrease the rates of SCI,<sup>92</sup> but the majority of studies were not able to identify electrical cardioversion as a risk factor for SCI.<sup>76,78,80,96</sup>

## Is there a need to reform anticoagulatory treatment regimes?

Kobayashi et al<sup>63</sup> showed in a patient group of 79 persons with AF that the CHADS<sub>2</sub> score was associated with the number of SCIs in cortex/subcortex. There was no correlation with other infarct locations. Reviewed by Kalantarian et al,<sup>29</sup> data showed a twofold-increased risk in the odds of SCI.

Anticoagulation is able to reduce symptomatic stroke or TIA significantly in patients with AF. The impact on prevention of SCI is unclear. Further studies are necessary to find out whether anticoagulation influences SCI and identify patients who benefit from anticoagulation or antiplatelet therapy.<sup>29</sup> There is low evidence that warfarin is not able to reduce brain volume loss in AF patients,<sup>16</sup> and differences in cognitive decline in AF patients between warfarin, aspirin, or no treatment could not be reported.<sup>97</sup> However, a statistically nonsignificant trend toward warfarin treatment versus aspirin

**Table 2** Summary of SCI studies after different ablation techniques of PVI

Ablation technology	Year	Study	Participants	Study design	MRI Sequences	SCIs	P-value
IRF vs PVAC vs CB	2011	Herrera Siklody et al <sup>75</sup>	74 (IRF 27; PVAC 24; CB 23)	Prospective, observational multicenter study	FLAIR, DWI	IRF 7.4% PVAC 37.5% CB 4.3%	P=0.003
IRF	2014	Di Biase et al <sup>76</sup>	428	Patients undergoing PVI (IRF)	FLAIR, DWI	Pre-PVI 43% (prevalence) Post-PVI 7.9% (incidence)	–
IRF vs PVAC vs CB	2011	Gaita et al <sup>77</sup>	108 (IRF 36; PVAC 36; CB 36)	Prospective observational	FLAIR, DWI	IRF 8.3% PVAC 38.9% CB 5.6%	P=0.002* P=0.001** P=0.5***
IRF vs CB vs LB	2014	Wissner et al <sup>78</sup>	86 (IRF 22; CB 20; LB 44)	Prospective observational	FLAIR, DWI	Pre-PVI 57% (prevalence) Post-PVI 12.8% (incidence)	P=0.00959
IRF and PVAC	2011	Deneke et al <sup>79</sup>	86	Prospective observational	FLAIR, DWI	Post-PVI 38% (incidence)	–
RA-PVI vs manual IRF	2012	Rillig et al <sup>80</sup>	70 (100% AF)	Consecutive patients with AF without TIA or stroke	FLAIR, DWI	Post-PVI 17% (RA-PVI 18% vs IRF 15%)	P=ns
IRF	2013	Martinek et al <sup>81</sup>	131 (100% AF)	Consecutive patients with AF under continued OAC	DWI	Post-PVI 12.2% (incidence)	–
CB vs IRF	2011	Neumann et al <sup>82</sup>	89 (100% AF)	Single-center study	DWI	Pre-PVI 12.3% Post-PVI 7.9% (incidence) (CB 8.9% vs IRF 6.8%)	P=ns
IRF vs CB vs LB	2013	Schmidt et al <sup>83</sup>	99 (100% AF)	Prospective observational	DWI	Post-PVI 22% (incidence) (IRF 24.2% vs 18.2% vs LB 24.2%)	P=ns
IRF	2006	Lickfett et al <sup>84</sup>	20 (100% AF)	Consecutive patients with paroxysmal AF	DWI	Post-PVI 10% (incidence)	–
PVAC (modified procedure)	2013	Wieczorek et al <sup>85</sup>	120 (100% AF)	Prospective observational (50% all electrodes activated vs 50% only two electrode pairs simultaneously activated)	DWI	Post-PVI 20% (incidence) (all electrodes 28.3% vs two electrodes 11.7%)	P=0.039
PVAC	2013	Wieczorek et al <sup>85</sup>	37 (100% AF)	Prospective observational	DWI	Post-PVI 27% (incidence) (44% in patients with electrode interaction (E1 and E10) vs 11% in patients without)	P=0.029
PVAC (three modifications)	2013	Verma et al <sup>86</sup>	60 (100% AF)	Prospective observational	FLAIR, DWI	Pre-PVI 60% with lesions Post-PVI 1.7% (incidence)	–

**Notes:** \*P-value IRF vs PVAC. \*\*P-value CB vs PVAC. \*\*\*P-value CB vs IRF.

**Abbreviations:** AF, atrial fibrillation; CB, Cryoballoon; DWI, diffusion-weighted imaging; E1, electrode 1; E10, electrode 10; FLAIR, fluid-attenuated inversion recovery; IRF, irrigated radiofrequency; LB, laser balloon; MRI, magnetic resonance imaging; ns, not significant; OAC, oral anticoagulation; PVAC, pulmonary vein ablation catheter; RA-PVI, robot-assisted pulmonary vein isolation; SCI, silent cerebral infarction; vs, versus; TIA, transient ischemic attack.

in one study<sup>98</sup> and a statistically nonsignificant trend toward OAC and decreased risk of dementia in another study have been reported.<sup>99</sup> Flaker et al<sup>100</sup> assumed that less effective OAC is associated with higher rates of cognitive decline and vascular events in patients with AF under OAC. Thus, DOACs with a higher time in therapeutic range compared to warfarin may prevent SCI.

On the other hand, it is not clearly defined if diagnosed SCI in cerebral asymptomatic AF patients should lead to an increase in CHA<sub>2</sub>DS<sub>2</sub>-VASc score of the subject, and thus this may result in a treatment with OAC only caused by diagnosis

of SBI. Gaita et al<sup>13</sup> reported SCI rates approximately 90% in AF patients, while 60% of these patients had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≤1, and thus no general recommendation for OAC treatment.<sup>13</sup> If this therapy regime would prevent strokes in AF patients, MRI screening in AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≤1 should be discussed.

## Conclusion

Studies showed that silent brain infarction correlate with impaired cognition, neurological deficits, and psychiatric disorder, as well as an increased risk of stroke. These suggest that

these findings are neither silent nor innocuous.<sup>101</sup> Especially in elderly people, prevention strategies should be intensified, with a particular focus on the treatment of hypertensive microangiopathy to minimize the risk of eroding brain function and acute stroke.<sup>22</sup> Targeted education on the warning signs of stroke and risk factor reduction efforts for individuals who report stroke symptoms may be helpful in improving early recognition and in the prevention of stroke.<sup>51</sup>

In studies, especially patients with AF had a higher rate of SCI and increased risk of stroke.<sup>56,102</sup> A possible cause is a synergistic effect of microthrombi and hemodynamic abnormalities.<sup>56</sup> Importance of prophylactic anticoagulation to reduce the incidence of SCI is unclear because of less data.<sup>29</sup> Periprocedurally occurring SCIs are five to ten times more common than strokes. Consequences for patients are not sufficiently analyzed. Investigation in different interventional techniques is necessary to improve patient's safety.

## Disclosure

The authors report no conflicts of interest in this work.

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