

Atrial Fibrillation Ablation and Reduction of Stroke Events: Understanding the paradoxical lack of evidence

Cover title: AF ablation and stroke

Sergio Barra MD¹⁻³, Kumar Narayanan MD PhD^{4,5}, Serge Boveda MD PhD⁶, Joao Primo MD², Helena Goncalves MD², Jakub Baran MD PhD⁷, Sharad Agarwal MD³, Eloi Marijon MD PhD^{4,8,9}, Rui Providencia MD PhD¹⁰

¹ Cardiology Department, Hospital da Luz Arrabida, V. N. Gaia, Portugal

² Cardiology Department, V. N. Gaia Hospital Center, V. N. Gaia, Portugal

³ Cardiology Department, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK

⁴ Cardiovascular Epidemiology, Paris Cardiovascular Research Center, Paris, France

⁵ Cardiology Department, MaxCure Hospitals, Hyderabad, India

⁶ Cardiology Department, Institute Pasteur, Toulouse, France

⁷ Division of Clinical Electrophysiology, Department of Cardiology, Grochowski Hospital, Postgraduate Medical School, Warsaw, Poland

⁸ Cardiology Department, European Georges Pompidou Hospital, Paris, France

⁹ Paris Descartes University, Paris, France

¹⁰ Cardiology Department, Barts Health Center, London, UK

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Introduction

Atrial fibrillation (AF) is the most prevalent chronic arrhythmia and a major cause of stroke and mortality. It is thought to confer an overall fivefold increased risk of a cerebrovascular event, causing approximately one third of all ischemic strokes. It has been demonstrated that half of the 2 to 3 fold higher risk of mortality among AF patients is related to AF itself, not only via fatal progression of heart failure, by far the most frequent mode, but also sudden death, stroke or peripheral embolic events (1, 2). Atrial fibrillation patients who suffer a cardioembolic stroke tend to have a worse age-adjusted outcome compared with stroke patients in the absence of AF. The prevalence of AF is on the rise worldwide, which highlights the importance of implementing measures aiming at detecting this sometimes silent condition and reducing the risk of complications associated with it.

Anticoagulation has been shown to effectively reduce the risk of a cerebrovascular event to a great extent. However, despite adequate anticoagulation, some patients remain at risk of stroke. Whether successful catheter ablation can reduce this risk remains unclear. Although there has not been any convincing evidence thus far that AF ablation leads to a reduction in the risk of stroke, no randomized study was powered to address this question. In this review paper, we discuss the AF-Stroke association, as well as the apparent lack of evidence supporting the use of ablation for the specific reduction of this endpoint.

The AF-Stroke Nexus

Although the notion of thrombus formation due to stasis of blood (mostly in the left atrial appendage), with subsequent embolism to the brain, has been and remains the generally accepted explanation for the increased risk of stroke in AF, fact is that the exact pathogenesis of stroke in AF patients remains unclear and much more complex, especially when considering the lack of temporality between AF episodes and stroke as observed in patients

with implantable loop recorders, and the increased risk of non-cardioembolic stroke which has also been reported in AF patients. Mechanisms such as large-artery atherosclerosis, endothelial dysfunction or cerebral small vessel occlusion, commonly seen in patients with AF, may also contribute to an increased risk of stroke among AF patients, confounding the association to some extent.

Recent attention has centred on the *atrial cardiopathy* hypothesis: this was elegantly described by Hooman Kamel and colleagues in their updated model of thromboembolic stroke (5). Briefly, the authors emphasised the importance of an abnormal atrial tissue substrate, or *atrial cardiopathy*, characterised by progressive chamber dilatation with ensuing fibrosis and impaired myocyte function, which subsequently results in AF and thromboembolism. The arrhythmia itself further increases the risk of thromboembolism and leads to additional adverse structural remodeling of the atrium, thereby worsening the *atrial cardiopathy* and further increasing the risk of stroke. However, the *atrial cardiopathy* as a cause of cardioembolic stroke appears to be independent of AF itself. Electrocardiographic markers of atrial dysfunction, such as an abnormally increased P-wave terminal force in lead V1, associate much more strongly with embolic, rather than with lacunar stroke due to small-vessel occlusion, regardless of the presence of AF (6).

Stroke Reduction by Catheter Ablation of AF

In the *Atrial Fibrillation Follow-up Investigation of Rhythm Management* (AFFIRM) (7) and *RAte Control versus Electrical cardioversion for persistent atrial fibrillation* (RACE) (8) trials, stroke rates did not differ significantly in the rate versus rhythm control groups. However, rather than suggesting a lack of benefit of a rhythm control strategy, both trials mainly highlighted the need for appropriate anticoagulation in the presence of risk factors for stroke. In both trials, cessation of anticoagulation therapy was allowed four weeks after

documentation of sinus rhythm, which may have led to increased risk of stroke and mortality in patients in the rhythm control arm. Moreover, they exposed the relative inefficiency of antiarrhythmic drugs in maintaining sinus rhythm (e.g. less than 40% AF-free survival in the RACE trial). Therefore, their results can hardly be extrapolated to the current era of AF treatment when the more effective catheter-based treatment of AF has become common.

Maintenance of sinus rhythm is unequivocally beneficial in patients with AF, with a sub-study of the AFFIRM trial showing that both oral anticoagulation and sinus rhythm were independently associated with a better survival and a 60% reduction in stroke risk (9). As ablation is superior to anti-arrhythmic drug therapy for maintaining sinus rhythm and reducing the burden of AF, it would seem logical that this approach could reduce stroke risk to some extent. Multiple studies have assessed whether catheter ablation can reduce the risk of stroke and/or mortality, and two recent meta-analyses (10, 11) pooled available data to provide further insight. With regard to the outcome of stroke, a reduction was noted only with observational studies (12-14), but the limitations of observational design need to be borne in mind. It is likely that patients in whom sinus rhythm can be maintained with ablation are inherently less prone to stroke given their more favourable risk profile and less advanced atrial cardiopathy. This limitation can be overcome only through rigorous randomization. However, no stroke reduction was noted in the pooled analysis of randomized trials in the two aforementioned meta-analyses.

Since the publication of the two meta-analyses on this topic (13, 14), there has been only one additional randomized trial addressing the question of whether AF ablation can impact on hard outcomes. This was in fact the largest ever randomized study on this topic, the *Catheter Ablation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA)* trial (15). Along with CABANA, there were a total of 17 randomized studies comprising 4,788 patients (2,519 receiving ablation vs. 2,269 on optimal medical therapy alone) and 13,279

patient-years of follow-up. The pooled data suggested that the absolute risk of stroke was very low, and practically identical in both the interventional and medical therapy groups (0.8% risk in the former versus 0.9% in the latter). It may appear paradoxical that available evidence does not lend support to the concept of reduction in stroke events by AF ablation, which may be logically expected, as mentioned earlier. In the following sections we put this seeming lack of evidence in perspective and discuss possible reasons why it may be difficult for AF ablation to have a demonstrable impact with respect to this endpoint.

The AF ablation procedure and anticoagulation protocol

In its most typical form, an AF ablation procedure involves access to the left atrium through one or two transseptal punctures and the electrical isolation of the pulmonary veins with radiofrequency energy, cryoablation or alternative sources of energy. In specific patients, more extensive ablation might be required, such as the ablation of complex fractionated atrial electrograms or ganglionated plexi or the performance of ablation lines. However, the effectiveness of these approaches in improving the outcome of the procedure remains a matter of dispute.

The anticoagulation protocol typically involves a minimum of one month of effective anticoagulation with either warfarin or one of the new oral anticoagulants (NOAC) prior to the ablation, plus at least 2 months after it. The decision to discontinue anticoagulation beyond 2 months post-ablation should not be based on the perceived outcome of the procedure, but rather on the patient's stroke risk profile. However, despite these precautions, the occurrence of an embolic stroke remains one of the most feared complications of an AF ablation. This could manifest as symptomatic or asymptomatic stroke or, most frequently, cerebral microembolism. The risk of silent embolism, as detected by cerebral MRI, can occur in up to 20 to 30% of patients even with uninterrupted anticoagulation therapy. The risk may

be higher in older patients, those with persistent AF (compared with paroxysmal) or submitted to electrical cardioversion or more extensive ablation.

The impact of stroke on AF-related mortality

In a sub-analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, only approximately 7% of deaths among AF patients on anticoagulation were due to stroke or peripheral embolism, with most deaths resulting from other cardiac causes or non-cardiovascular conditions (2). Similar findings were noted in a large observational study of patients diagnosed with AF in a four-hospital institution (16). Likewise, in a more comprehensive analysis of contemporary AF trials, most follow-up deaths were seen to be cardiac-related, whereas non-hemorrhagic stroke and systemic embolism represented only 5.7% of the total mortality (17). Perhaps unsurprisingly, stroke or peripheral embolism also represents only a small percentage of in-hospital deaths amongst hospitalised patients with AF (18).

Approximately half of deaths reported in AF patients are cardiovascular in nature, while one third die of non-cardiovascular causes and the remaining die from stroke or haemorrhage (around 6% each), or other less prevalent causes. Thus, the apparent survival benefit of AF ablation in specific groups of patients, as seen in AATAC and CASTLE-AF, and as suggested by some sub-analyses of CABANA, is likely the result of a reduction in heart failure-related death or the interruption of potentially deleterious antiarrhythmic drug therapy rather than a reduction in stroke-related mortality. This notion is supported by the recent *Catheter Ablation Versus Medical Rate control in Atrial Fibrillation and Systolic Dysfunction* (CAMERA-MRI) study, which demonstrated that restoration of sinus rhythm with catheter ablation results in significant improvements in ventricular function in persistent AF patients with idiopathic cardiomyopathy (19). Successful AF ablation may indeed lead to

improvements in left ventricular function (20, 21), particularly when sinus rhythm is maintained (21).

Low number of Stroke events in Contemporary AF Populations

In all 17 randomized studies comparing the risk of stroke (or death) in AF ablation patients versus those treated medically, only 41 stroke events were reported, translating into an unadjusted stroke rate of only 3 per 1000 patient-years in the ablation group and 3.2 in patients treated medically. The *Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation* (CASTLE-AF) (22) and CABANA (14) trials accounted for 29 stroke events, with the remaining 15 trials reporting only 12 strokes in total. Contrarily, mortality rates were five to seven times higher, at 14.5 and 21.2 per 1000 patient-years in ablation and medical therapy groups, respectively, translating into a much lower number needed to treat. In CABANA, the number of deaths was approximately twenty and ten times higher than the number of disabling strokes in the ablation and control groups, respectively. Accordingly, in the intention-to-treat analysis there was a non-significant 15% relative reduction in the mortality hazard. **Although the reader should take into account that outcome data in randomized trials is not always representative of “real world” data, some studies have shown that the rates of stroke in “real world” patients are actually consistent with those seen in landmark randomized trials such as ROCKET-AF and RE-LY.**

Most patients considered for AF ablation have a low annual stroke risk regardless of whether they are actually ablated, provided they are appropriately anticoagulated as per their CHA₂DS₂-VASc scores. Ben Freedman and colleagues showed that AF patients on anticoagulation have a stroke risk similar to that of non-AF patients, and the residual stroke risk likely reflects the occurrence of noncardioembolic stroke that may be expected in

individuals of similar age, sex and comorbidity without AF rather than anticoagulant treatment failure (23). Conversely, this finding did not apply for overall death in their study, as AF was associated with a direct mortality risk that was only partially reduced by anticoagulant therapy (23). These results again help explain the more noticeable effect of catheter ablation on mortality risk compared with an apparently limited effect on the risk of stroke. If adequate anticoagulation already reduces AF-related stroke to a large extent, it would be quite difficult to prove a further incremental benefit of catheter ablation in the reduction of residual stroke risk. For instance, if catheter ablation reduced stroke risk by 50%, which would be quite commendable, the NNT to prevent one stroke event would still be very high based on a baseline overall absolute risk of 0.9% in medically treated patients, as seen in randomized data. This helps explain why no randomized study to date was powered to show any meaningful effect of AF ablation on stroke rates, and even pooled data lacks statistical power. Furthermore, it shows how a different metric such as the NNT can sometimes provide a more realistic estimate of how useful an intervention can be compared with relative measures of risk. The very low incidence of stroke in randomized studies is in fact quite reassuring, although caution is required when extrapolating to *real-world* patients.

Cardioembolic versus noncardioembolic stroke

Is AF always a culprit for stroke in patients with atrial fibrillation (24)? This subject has been addressed by different investigators (24, 25), although most clinical trials on the risk of stroke in AF have not distinguished between the different stroke mechanisms. It has been estimated that between one sixth and one third of classifiable cerebral infarcts are unrelated to AF and have characteristics suggestive of a non-cardioembolic mechanism (24, 25). Large-vessel atheromatosis, in particular, that affecting the carotid arteries, and cerebral small vessel disease may be the cause of stroke, although the distinction between the different

pathophysiologic mechanisms of stroke remains a difficult task. The proportion of cardioembolic stroke is significantly lower in patients on anticoagulation, while the proportion of noncardioembolic stroke is lower in those taking aspirin (25). Most importantly, and as mentioned before, cardioembolic stroke rates are sharply reduced by adjusted-dose warfarin - a reduction in excess of 80% compared with aspirin (25). A recent study has shown that a 1% increase in anticoagulant use associates with a 0.8% decrease in the weekly rate of AF-related stroke (26). Essentially, stroke rates in adequately anticoagulated AF patients are similar to those of patients without AF (23) – the residual stroke risk is mainly due to noncardioembolic stroke, for which the effectiveness of oral anticoagulation has been disputed.

Although successful catheter ablation may in theory reduce the risk of cardioembolic stroke by preventing thrombus formation due to stasis of blood in the context of AF, there is no reasonable pathophysiologic mechanism through which AF ablation could reduce the risk of noncardioembolic stroke. Considering that most patients submitted to AF ablation have a CHA₂DS₂-VASc score between zero and 3, their estimated annual risk of stroke off anticoagulation would vary between 0.2% and 3.2%. The risk of cardioembolic stroke, corresponding to between two thirds and five sixths of that number, can be drastically reduced with consistent anticoagulation, leaving a residual annual stroke risk of up to 0.5-0.6% consisting mostly of noncardioembolic events. Lifestyle modification, including aggressive treatment of vascular risk factors and concomitant comorbidities such as hypertension, sleep apnoea, diabetes mellitus, dyslipidaemia and obesity is thus more likely to impact on the residual risk of stroke rather than catheter ablation.

Cardioembolic stroke in appropriately anticoagulated patients

Atrial fibrillation patients on adequate anticoagulation have a stroke risk which is similar to that of non-AF patients (26). However, the potential for stroke still remains, as described above. Although it is reasonable to speculate that most of these events represent noncardioembolic stroke events, the detection of left atrial appendage (LAA) thrombus in a non-negligible percentage of appropriately anticoagulated patients suggests the potential for cardioembolic stroke, albeit very low, still remains. Several studies have shown that AF patients on adequate anticoagulation not infrequently develop LAA thrombus, as detected through transesophageal echocardiography. The probability of LAA thrombus formation is higher in patients in persistent AF, with higher CHA2DS2-VASc scores, increased left atrial size, reduced LAA flow velocity and decreased left ventricular systolic function. On the other hand, in patients without any risk factor the incidence of LAA thrombus approaches zero. It is therefore highly recommendable that LAA thrombus is excluded in patients with clinical features associated with increased cardioembolic risk, and that the decision to anticoagulate post-AF ablation takes into account not only the CHA2DS2-VASc score of the patient but also left atrial size and function.

Asymptomatic cerebral emboli

Generally speaking, randomized studies accounted for neither asymptomatic stroke nor cerebral microembolism, which may represent the majority of cerebrovascular events in AF patients. Contrary to the strategy of anticoagulation cessation in AFFIRM (7) and RACE (8), most AF patients undergoing ablation continue their anticoagulation indefinitely according to their CHA2DS2-VASc score. Asymptomatic embolic signals, as detected by transcranial Doppler, have been shown to predict stroke risk in acute stroke, symptomatic carotid stenosis and postoperatively after carotid endarterectomy (27). Although the incidence of cerebral microembolic signals during endocardial ablation procedures has been previously examined

(28), whether AF ablation reduces the long-term risk of cerebral microembolism has never been assessed before, but given the possible association between AF and increased risk of dementia (29), such a study could provide important insights. There is an increasing body of evidence associating AF with cognitive decline and/or dementia, possibly the result of recurrent asymptomatic cerebral thromboembolism. Notwithstanding, any potential impact on long-term silent thromboembolism must be weighed against the procedural risk of stroke and asymptomatic thromboembolism, the latter of which occurs in a substantial percentage of patients and is mostly related to procedural parameters such as the activated clotting time value and performance of electrical cardioversion (30). The long-term implications of an accumulated burden of neurological injury from intracardiac interventions such as catheter ablation are unknown.

Recurrences of atrial fibrillation following catheter ablation

Atrial fibrillation recurrence rates of up to 54.5% were reported in AF trials (e.g. 36.9% in CASTLE-AF and 52% in CABANA), which means that, although catheter ablation was fairly successful in reducing AF burden, many patients were still experiencing AF. Importantly, as most AF episodes are asymptomatic, intermittent monitoring alone is inadequate in assessing AF burden, and estimates of AF control in randomized trials which did not use continuous monitoring likely overestimate the efficacy of ablation or antiarrhythmic drug therapy.

Research has shown that even short episodes of atrial arrhythmia associate with increased stroke risk, and thus very high AF-free survival rates may be required to significantly reduce the risk of stroke.

Adverse Atrial Remodeling

Although AF ablation may significantly reduce AF burden, thereby theoretically preventing some cardioembolic events, it does not fully reverse the process of reverse remodeling, nor does it satisfactorily control the systemic risk factors associated with non-cardioembolic stroke. It is possible that the atrial cardiopathy per se plays a bigger role in the pathophysiology of AF-related stroke than AF itself (AF thereby being merely a marker of that condition). Atrial structural and electrical remodeling are associated with increased automaticity and triggered activity and subsequently recurrent arrhythmia, but also increased risk of thromboembolism. Pre-ablation atrial fibrosis associates with increased risk of arrhythmia (31), and may be a predictor of stroke during follow-up. In fact, more severe left atrial late gadolinium enhancement associates with increased risk of major adverse cardiovascular and cerebrovascular events, driven primarily by increased risk of stroke or TIA (32).

Final remarks

Summarizing, current randomized data do not demonstrate a clinically impactful reduction in stroke risk through AF ablation. The reasons for this are manifold. Firstly, absolute stroke rates are very low in appropriately anticoagulated contemporary AF populations, hence even large relative reductions in stroke risk would still translate into a tiny net benefit. Secondly, residual stroke risk may largely relate to non cardioembolic stroke wherein AF ablation cannot be expected to show benefit. Thirdly, even occasional, short, potentially silent AF recurrences post “successful” AF ablation may still matter as far as stroke risk is concerned. Lastly, adverse atrial remodelling (atrial cardiopathy) is likely a dominant factor in stroke risk, relatively unimpacted by ablation. A relatively unexplored area is the issue of silent cerebral microembolism with attendant cognitive impairment, and further research should focus on whether AF ablation has any long term impact in this regard. In conclusion, it

appears unlikely that a randomized trial can be adequately powered to show meaningful reductions in stroke risk by AF ablation, considering low absolute event rates, although the ongoing Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST, NCT01288352) trial may provide some needed clarity in this area. Thus, pragmatic discussions on the long term value of AF ablation should move away from a stroke centric approach and rather focus on the potential reduction of cardiovascular mortality and hospitalization (for which there is increasingly encouraging evidence). With the ready availability of reliable anticoagulation with NOACs, interventions beyond stroke-reduction measures are clearly warranted to meaningfully reduce total mortality in this population (**Figure 2**).

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FIGURE LEGENDS

Figure 1 – Forest plots comparing ablation vs. medical treatment alone for the prediction of stroke (top) and mortality (bottom)

Figure 2 – Treatment options for the different stages of the atrial cardiopathy. * Risk factors include arterial hypertension, diabetes mellitus, dyslipidaemia, obesity, sleep apnoea, and any other conditions potentially associated with endothelial dysfunction and atrial fibrillation.

LAAO – Left atrial appendage occlusion; OAC – Oral anticoagulation