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EDITORIAL

Oral anticoagulation after catheter ablation of atrial fibrillation: caught in the attribution trap?

Paulus Kirchhof[1,2,3]*, Yanish Purmah[1], and Atul Verma[4]

[1]University of Birmingham Centre for Cardiovascular Sciences, Clinical and Integrated Cardiovascular Sciences, and SWBH NHS trust, Birmingham, UK; [2]Atrial Fibrillation Competence NETwork (AFNET), Münster, Germany; [3]Department of Cardiovascular Medicine, Hospital of the University of Münster, Münster, Germany; and [4]Southlake Regional Health Centre, Heart Rhythm Program, Newmarket, Ontario, Canada

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This editorial refers to 'Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark'†, by D. Karasoy *et al.*, on page 307.

Catheter ablation procedures are performed in ~5-10% of patients suffering from atrial fibrillation (AF).[1–3] While the main reason for undertaking AF ablation is because the patient is suffering from symptomatic AF, those who undergo AF ablation are younger and 'generally healthier' than patients who do not undergo ablation treatment,[4–6] as reflected by lower stroke risk scores, but also driven by confounders that will inform the clinical decision to submit a patients to catheter ablation procedures.

Manipulation in the left atrium, wound healing, and scar formation in the atria, along with other factors, generate a thrombogenic milieu in the atria of patients undergoing AF ablation. Therefore, all ablation patients require continuous oral anticoagulation during and for at least 3 months after an AF ablation procedure. The indication for long-term anticoagulation should be based on clinical stroke risk factors thereafter.[7,8]

Karasoy and colleagues have now reported on a cohort of 4050 patients (59.5 years, 74% men) who underwent a first catheter ablation for AF in Denmark from 2000 to 2011.[6] Approximately half of the patients had clinically documented AF recurrence (measured by hospitalization or reablation) and each patient received 1.5 AF ablation procedures on average, very much in line with published outcomes after catheter ablation. The authors furthermore analysed thrombo-embolic events [(ischaemic stroke, transient ischaemic attack (TIA), and peripheral artery embolism] and severe bleeding events in this cohort over a mean follow-up time of >3 years. This information is valuable because of the comprehensive capture of information in a population-based sample. Consistent with other data,[9] early thrombo-embolic events after ablation were common (20 thrombo-embolic events in the first 2 weeks after the first ablation, corresponding to an estimated yearly incidence of 12.9% per year; figure 2 in Karasoy *et al.*[6]). It is conceivable that changes in practice, e.g. continued oral anticoagulation during AF ablation procedures,[7,8] prevent some ischaemic strokes during AF ablation.[10] Clearly, there is an unmet need to better protect the brain against ischaemic damage during AF ablation.[11]

Half of the patients received oral anticoagulation for at least 1 year after catheter ablation, including patients without a clear indication for continued anticoagulation (56% of $CHA_2DS_2VASC = 0$ patients, 67% of $CHA_2DS_2VASC = 1$ patients[8]). As expected, bleeding events were higher in patients who remained on anticoagulation after AF ablation [hazard ratio (HR) 2.05; figure 4 in Karasoy *et al.*[6]]. There were 103 clinically documented thrombo-embolic events during follow-up (annualized rate 0.8%, wide confidence intervals), numerically a bit lower than expected. In part, this lower rate is probably explained by the low intensity follow-up, where patients with 'subclinical' strokes and TIAs that are managed as outpatients or not brought to medical attention will not be captured on national databases, while controlled trials will pick up such events. Furthermore, permanent 'silent brain emboli' which are found in AF[12] and can be triggered by catheter ablation[9] are not reflected in this analysis, although they may contribute to cognitive decline.[9] Nonetheless, the stroke rate in a matched cohort of Danish patients receiving cardioversions or antiarrhythmic drug therapy during the same period was higher (1.77% per year). Our hypothetical figure summarizes these observation in a speculative manner (*Figure 1*).

Can we attribute lower stroke rates to AF ablation?

In short, we do not know the answer to this question, and only properly planned and conducted interventional trials can reveal this. Patients who discontinued oral anticoagulation in the study of Karasoy *et al.* had numerically more thrombo-embolic events

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* Corresponding author. University of Birmingham Centre for Cardiovascular Sciences, Clinical and Integrated Cardiovascular Sciences, School of Clinical and Experimental Medicine and SWBH NHS trust, IBR, 1st Floor, Birmingham B15 2TT, UK. Tel: +44 121 4147042, Email: p.kirchhof@bham.ac.uk

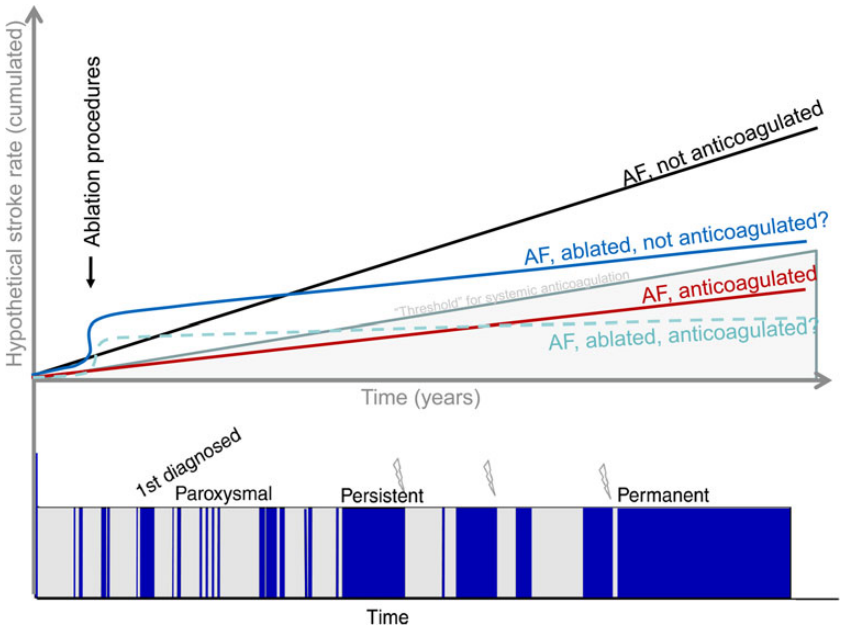

Figure 1 Hypothetical rates of ischaemic stroke in patients with atrial fibrillation (AF), in patients with and without catheter ablation, based on the unproven assumption post-ablation stroke risk is reduced. The black line shows the stroke rate of general AF patients; the red line the stroke rate in anticoagulated AF patients (65-70% reduction in stroke). The dark blue line illustrates a hypothetical stroke rate in AF patients undergoing AF ablation but not receiving long-term anticoagulation, assuming that the procedure (i) induces periprocedural strokes and (ii) reduces long-term stroke risk. The light blue line illustrates a hypothetical stroke rate in AF patients undergoing AF ablation and receiving anticoagulation. The grey triangle suggests the threshold for oral anticoagulation, weighing up stroke and bleeding risk. It is worthwhile to note that this threshold may be different depending on the bleeding risk induced by the anticoagulant of choice.

compared with those who continued anticoagulation (HR 1.42, wide confidence intervals; figure 4 in Karasoy *et al.*[6]). The baseline stroke risk of the cohorts was too heterogeneous to draw conclusions from this. Other data sets also report relatively low stroke rates in AF ablation patients.[13] While this may be due to a protective effect of ablation, it is also possible that unidentified confounding factors, aggregated in a clinical impression of vitality, leave patients suitable for catheter ablation at reduced stroke risk *per se*. This latter point is supported by the relatively low stroke risk in Danish ablation patients irrespective of ablation success.[6] However, while ablation may not be entirely successful, reduction in AF burden or a change in the pattern of AF (paroxysmal vs. persistent, AF or sinus rhythm at baseline) may affect stroke risk,[14,15] in line with the intuitive assumption that less time in AF may correspond to a lower risk of cardiac embolism.

'Known knowns' and 'unknown unknowns'

There is a simple lesson to learn from the report by Karasoy *et al*. Do not continue anticoagulation in AF patients beyond 3 months after ablation if they are not at risk for stroke ($CHA_2DS_2VASC = 0$). This is in line with current clinical guidance, and has the potential to avoid many bleeding events after AF ablation. Secondly, the present report, put in context, supports an emerging hypothesis that rhythm control therapy, especially AF ablation, may reduce stroke risk in AF. Ongoing trials such as EAST (www.easttrial.org, NCT01288,352) or CABANA (www.cabanatrial.org, NCT00911,508) will address the prognostic impact of rhythm control therapy including AF ablation including the effect of rhythm control therapy on stroke, on top of anticoagulation. Other trials are needed to define the optimal anticoagulation during AF ablation procedures in an era where novel anticoagulants are increasingly used. In addition, the data reported by Karasoy *et al*. suggest that further studies should be initiated to test whether oral anticoagulation can be modified (or even stopped) after successful catheter ablation of AF (e.g. OCEAN, NCT02168,829). Until we have seen the outcome of such trials, our present treatment pattern to continue oral anticoagulation after catheter ablation of AF in patients at risk for stroke should continue.

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