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Silent Cerebral Events during Catheter Ablation for Atrial Fibrillation:

Not Yet to Be Forgotten

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Transcatheter ablation (TCA) is an effective approach for treating atrial fibrillation (AF) refractory to antiarrhythmic drugs. The main TCA aim is maintenance of sinus rhythm with a consequent reduction of symptoms and thromboembolic events. Within the complications described, however, ischemic embolic accidents are unfortunately still not rare; in fact, also in updated series, neurological complications as stroke or transient ischemic attacks (TIA) are reported around 1%¹.

In addition, the use of post ablation cerebral magnetic resonance imaging (MRI) has proven that AF TCA may also cause asymptomatic cerebral infarctions (ACI) and these events relate to cognitive decline². Since first description^{3,4}, in fact, ACI have been reported widely, documented in up to 40% of the patients undergoing AF TCA.

A clear definition of these events, namely called silent cerebral infarctions (SCI), silent cerebral lesions (SCL) or asymptomatic cerebral infarctions (ACI), is the first required step to standardised literature reporting. Given this, despite several unsolved open issues⁵, it is to date clear that prevalence of ACI following TCA of AF relates to ablation tool^{6,7,8} and procedural protocol⁹. In fact, in an ideal setting, performing AF TCA by irrigated focal radiofrequency in patients not discontinuing warfarin (and with a “therapeutic” INR) and receiving heparin bolus before transseptal catheterization (aiming to an ACT above 300 seconds) has proved to reduce the risk of ACI down to 2%. If such a result could have potentially led to abolish the need of further assessing the topic, the recent clinical shift to the use of direct oral anticoagulants in the management of AF patients requires new evidences.

In this perspective the work by Kimura and colleagues introduces several inputs. In this well designed randomized study the Authors have compared uninterrupted rivaroxaban and warfarin as prophylaxis against TCA-induced ACI. In total 127 patients were randomized, 64 and 63 to the rivaroxaban and warfarin groups, respectively. The incidence of TCA-induced ACI at 24-hour cerebral MRI was overall 15.7%, similar for the rivaroxaban (15.6%) and warfarin (15.9%) groups. On top of this, no thromboembolic events occurred and no differences in major or non-major

bleeding emerged between study groups (3.1% vs. 1.6% and 18.8% vs. 19.0%, respectively). At multiple regression analysis, in addition, the only parameters relating to ACI incidence were previous deep and subcortical white matter hyperintensity (odds ratio, OR, 5.32, $p=0.002$) and frequency of electrical cardioversions during the procedure (OR 1.25, $p=0.016$).

The results of this study call for attention to a relevant clinical message. To date, ACI is defined as an acute new MRI-detected brain lesion in a patient without clinically apparent neurological deficit. A hyperintense lesion at diffusion-weighted MRI (DWI) indicates cellular edema in acute ischemia within minutes after its onset. The apparent diffusion coefficient map (ADC-map) of a diffusion-positive lesion is reduced, which prevents over-detection shine-through effects on DWI. A hyperintense DWI lesion (diffusion-positive) and a corresponding reduced ADC map (hypointense), therefore, represent the cornerstone for detecting new onset cerebral ischemias. In contrast, the T2-weighted fluid attenuated inverse recovery sequence (FLAIR) has been shown to turn positive only with delay, and FLAIR positivity is related to the volume of DWI-hyperintensity¹⁰. In the study by Kimura and colleagues cerebral lesions have been carefully assessed, as clearly supported by the excellent degrees of inter-observer reproducibility obtained, however definitions included dimensions cut-offs: ≥ 2 mm for lacunar infarctions, ≥ 3 mm for deep and subcortical white matter hyperintensities. The medical community is therefore in great need, to permit homogeneous comparisons within patients, ablation tools, and techniques of a standardized, unanimously accepted, cerebral MRI ACI definition, both for 1.5 and 3 Tesla scans. In fact, in the meantime, comparisons within studies and/or imaging techniques warrant caution.

Another point emerging from the work by Kimura and colleagues is the relevant impact that patient selection and clinical management have on description of ACI incidence. In this study the Authors included patients with left atrial diameter below 55 mm, and this is known to reflect a population exposed to a lower risk of thromboembolic events¹¹. On the other side, according to National Japanese guidelines, patients at a high bleeding risk, based on a creatinine clearance of 30–49

mL/min, an age above 75 years, or weighing less than 50 kg, received a reduced Japanese-approved 10-mg once daily rivaroxaban dose. Warfarin, instead, in patients aged above 70 years, received a controlled dose to attain INR above 1.6, and not the standard 2.0¹². These factors plausibly influence the description of the events, the first potentially under estimating, and the second over estimating, ACI incidence compared to experiences performed in other European or North American countries recommended towards different rivaroxaban daily doses and/or following other clinical guidelines. In fact, in the present study, the outcome of patients at high bleeding risk clearly calls for attention. In the rivaroxaban group, ACI were reported in 7/57 (12.3%) and in 2/6 (33.3%) patients receiving 15 and 10 mg daily rivaroxaban doses, respectively. In the warfarin group, instead, ACI were observed in 7/55 (12.7%) and in 3/8 (37.5%) patients with INR target of 2.0 and 1.6, respectively. The high bleeding risk patients managed by reduced drug dose or lower INR target, therefore, although not reaching statistical significance due to the limited number of cases involved, suffered a roughly 3 times greater risk of ACI incidence. This finding has unconceivable potential clinical interest and needs to be investigated in further larger clinical trials, also stratifying the population on the widely used HAS-BLED bleeding risk score¹³.

Eventually a relevant AF TCA procedural protocol indication emerges from the study by Kimura and colleagues. Electrical cardioversion at the end of the procedure, performed, as in most electrophysiology laboratories in case sinus rhythm is not restored by catheters, was significantly more often performed in patients who developed ACI. For patients managed with anticoagulant interruption or uninterrupted warfarin controversial reports on this issue are available; a previous study, however, was designed to investigate the benefits, in terms of ACI, of postponing electrical cardioversion of persisting AF from the end of the procedure to after 4 weeks of therapeutic anticoagulation. In this experience the incidence of ACI resulted reduced from 38% to 13%¹⁴. Given that the main goal of AF management is to reduce the likelihood of ischemic cerebral events, further research should carefully focus on possible strategies to reduce also the incidence of silent

thromboembolism during AF TCA, to confirm, for example, if with uninterrupted direct oral anticoagulants electrical cardioversion should absolutely be avoided.

In conclusion, despite the relatively low incidence of symptomatic stroke following AF TCA (1%), the evidence of ACI is worrisome in a population already at high risk for cerebral embolism and dementia. Considering that post-procedural MRI lesions are in any case a sign of brain damage, even if asymptomatic or not detected in follow-up MRI, and that a significant amount of patients will need an additional ablation procedure while pursuing rhythm control, their possible impact cannot be ignored. In this respect the study by Kimura and colleagues introduces clinically highly relevant data, however, more research on the topic is surely needed.

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