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The quest to refine atrial fibrillation-related stroke risk stratification: could the answer lie in left atrial appendage angiography?

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Prevention of stroke and thromboembolic events in atrial fibrillation (AF) remains one of the pillars of AF management, as recommended by guidelines[1,2]. Stroke prevention relies upon an accurate stroke risk assessment to guide the need for oral anticoagulation, with the CHA_2DS_2-VASc score being the most commonly used risk factor-derived score. The score is based on the presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, vascular disease, age 65-74 years, and sex category (female).

The CHA_2DS_2-VASc score, like any other condition-specific risk score, must balance ease of use with accuracy and, as such, performs well at identifying patients at low risk of ischaemic stroke and mortality (i.e., males with a CHA_2DS_2-VASc score of 0, or females with a score of 0 or 1), with modest performance in higher-risk patients. Whilst international guidelines do not currently support the routine integration of biomarker-derived measurements (whether from urine, blood, or imaging) into AF-related stroke risk stratification, the quest to refine these risk scores by identifying appropriate biomarkers (whether urine-, blood- or imaging-based) continues[3,4].

In this issue of EuroIntervention, Jiang and colleagues present the findings of a single-centre, retrospective study examining the association between stroke risk and left atrial appendage (LAA) mechanical function. To determine the LAA ejection fraction and LAA contrast retention, the LAA mechanical function is assessed invasively by LAA angiography with contrast injection using a pigtail catheter in patients undergoing LAA occlusion[5]. Contrast retention was classified according to the number of cardiac cycles required to clear the LAA of contrast on cine angiography: grade 1 in less than 3 cycles; grade 2 within 3 to 6 cycles; grade 3 in more than 6 cycles. Of the 746 patients included in the analysis, 20.2% had a prior history of stroke ("stroke group"), and 79.8% had no prior history of stroke ("control group"). The angiography-derived LAA ejection fraction was significantly lower in the stroke group (14% vs 20%), due to a larger LAA end-systolic area. Contrast retention differed significantly between the 2 groups: in

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the stroke group, 4% of patients had grade 1, 29.1% had grade 2, and 66.9% had grade 3, compared with 33.4%, 32.6%, and 33.9% for the respective grades in the control group. Multivariate analysis showed contrast retention to be independently correlated with a prior history of stroke. Moreover, receiver operating characteristic analysis showed that the combination of contrast retention and the CHA_2DS_2-VASc score provided the best discrimination ability in identifying patients with a prior history of stroke (C-statistic=0.871 vs C-statistic=0.829 for CHA_2DS_2-VASc score alone; p=0.048).

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By being the largest study to identify angiography-derived LAA contrast retention as an imaging-based biomarker, along with the potential to ameliorate stroke risk classification in AF, the present study is noteworthy. Nonetheless, it is imperative to acknowledge its limitations. First, the retrospective and cross-sectional nature of the analysis, with retrospective determination of "stroke" and "control" groups based on historic stroke, highlights the need for prospective validation of LAA mechanical function assessment before its integration into existing stroke risk scores. Second, the C-statistics comparing the combination of contrast retention and CHA_2DS_2-VASc score versus CHA_2DS_2-VASc score alone may be statistically significant (only just), but the point estimates are marginally different, and the 95% confidence intervals (not provided) are likely to overlap. Indeed, statistical significance does not mean clinical or practically meaningful significance. Third, even if angiography-derived LAA contrast retention were to be prospectively validated in future studies, the benefits in terms of stroke risk reduction would need to significantly outweigh the procedure-related costs and risks, which include vascular access- and transseptal-related complications, thromboembolic risk, and angiography-related pericardial effusion. In asymptomatic individuals, it is inconceivable that an invasive procedure of this nature would be acceptable to either the patient or physician, on both clinical and financial grounds.

However, one cohort in whom the benefits of LAA angiography may outweigh the risks is those undergoing clinically driven AF catheter ablation. For example, in 2 patients undergoing AF ablation, both with a CHA_2DS_2-VASc of 0 in males (or 1 in females), the first with grade 1 contrast retention and the second with grade 3, the former may, hypothetically, be able to safely discontinue long-term anticoagulation following ablation, thus avoiding bleeding-related complications; whereas, the latter may benefit from continuation of anticoagulation. In patients undergoing AF ablation, LAA angiography is, arguably, of minimal additional risk as vascular and transseptal access have already been secured, although the risk of angiography-related pericardial effusion remains and would require informed consent[6]. Given that most AF patients are clinically complex, with multimorbidity and polypharmacy[7], such a patient subgroup may be small.

In addition, several studies have shown that some LAA morphologies, especially "cauliflower" and "windsock" shapes, may be associated with a higher thromboembolic stroke risk in AF[8,9]. The lack of systematic LAA morphology assessment in this current study feels like a missed opportunity.

Given these limitations, invasive haemodynamic assessment of LAA mechanical function is unlikely to yield the answer to refining AF-related stroke risk classification, except perhaps in high-risk cohorts already undergoing catheter ablation. Risk is also dynamic, changing with ageing and incident comorbidities – so a "one-off" risk assessment is insufficient, and repeated reassessment is needed. However, and most critically, this study adds weight to the hypothesis that non-invasive assessment of LAA mechanical function, specifically LAA contrast retention, such as by computed tomography angiography, may improve the performance of current risk scores without the additive risks of an invasive procedure, encouraging further prospective study in this field. Finally, stroke prevention is only one aspect of the holistic or integrated-care approach to AF management, which also necessitates early rhythm control in selected patients and attention to comorbidities and lifestyle factors[10]. Adherence to such an evidence-based approach has been associated with improved clinical outcomes[11].

Conflict of interest statement

G.Y.H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Anthos, for which no fees are received personally. G.Y.H. Lip is a NIHR Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 899871. D. Gupta reports proctor fees for left atrial appendage occluder implants from Abbott Ltd. M.T. Mills has no conflicts of interest to declare.

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