How should we manage left atrial thrombosis?

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Abbreviations: AF, atrial fibrillation; CHA_2DS_2-VASc, Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); LA, left atrial/left atrium; LAA, left atrial appendage; LAA, left atrial appendage; LASEC, left atrial spontaneous echo contrast; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; RCT, randomized controlled trial; TEE, transoesophageal echocardiography; VKA, vitamin K antagonist.

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Intra-atrial thrombus is usually associated with atrial fibrillation (AF), with up to 90% of cases developing within the left atrial appendage (LAA) in the absence of rheumatic valve disease; when rheumatic valve disease is present, the thrombus is localized in the left atrial (LA) cavity in 50% of cases [1]. Thromboembolism is the most feared complications of intra-cardiac thrombosis [2].

Evaluation of the LA and LAA for the presence of thrombus and severe spontaneous echocardiographic contrast (LASEC) before cardioversion and pulmonary vein isolation is based on transoesophageal echocardiography (TEE). Computed tomographic angiography has demonstrated diagnostic accuracy similar to that of TEE for the detection of thrombus [3,4].

Risk factors for LA/LAA thrombus include hypertension, heart failure, older age, structural heart disease or cardiomyopathy, persistent versus paroxysmal AF, and higher CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]) score [5]. Other factors that can predict or are associated with LAA thrombi include higher D-dimers levels, B-type natriuretic peptide levels, von Willebrand factor, enlarged LA size, low LAA velocities, and dense LASEC detected within the LA/LAA [6]. In a retrospective single-centre study, the presence of moderate/severe LASEC was an independent predictor of stroke or death at 5-year follow-up in patients with non-valvular AF. However, the inclusion of LASEC in stroke risk scores may modestly improve risk stratification [7].

Still, the optimal antithrombotic management of such a clinical issue is not established. In this issue of the journal, Calabro et al., on behalf of the Working Group of Thrombosis and the Working Group of Interventional Cardiology of the Italian Society of Cardiology, present a review on the use of non-vitamin K antagonist oral anticoagulants (NOACs) in the setting of AF with LA thrombosis [8]. The authors acknowledge that the level of evidence is still relatively low for NOACs in patients with atrial/LAA thrombosis compared with the many randomized controlled trials (RCTs) on NOACs for stroke prevention in AF and more recently on their use in cardioversion. This is, however, a clinical issue for which clinicians wish to read what is available in the literature, and also clinical perspectives. The main message is that, although evidence is still sparse and related to observational data with small numbers, as NOACs are easier to manage and have a better safety profile than vitamin K antagonists (VKAs), they represent an attractive alternative in the challenging scenario of atrial thrombosis. The rate of thrombus resolution with NOACs ranged from 60% to 100%, and was inversely associated with the number of cases in the series, highlighting the need for large,

prospective studies in this field. The largest number of patients and the main information in the review came from the X-TRA study, which included 53 patients in the analysis [9]. Considering that NOACs are now recommended as first-line therapy in most AF patients (in the absence of contraindications) [10], their initial use might, however, be considered as a default strategy in most cases with documented LA/LAA thrombus.

Detection of LA thrombosis may be considered as a demonstration of anticoagulant resistance or failure that would need a more effective anticoagulation strategy. Taking into account the baseline or previous antithrombotic therapy is thus a main aspect when deciding on the subsequent management of these patients. Switching from a VKA to a NOAC, prescribing a standard rather than a reduced dose of NOAC (if this is possible, taking into consideration renal function), switching from one NOAC to another NOAC, switching from a NOAC to a VKA, and/or increasing the target international normalized ratio to between 3 and 4, are all possible options. These strategies could be tested sequentially, every 4–6 weeks, with repeated imaging. The risk of stroke is likely to be lower in patients who have not had a thromboembolic event after initiation of these therapeutic options, because one usually considers that an “old” and organized thrombus is less likely to break up. NOACs offer several advantages over VKAs in this context. Unlike VKAs, which can take between 36 and 72 hours to obtain an effective anticoagulant effect, NOACs have a rapid onset of action and reach peak plasma concentrations within 2–3 hours of administration, which may be useful for treating an active thrombus, whereas this point may be less relevant for preventive anticoagulation. NOACs have more predictable pharmacokinetic and pharmacodynamic profiles, thus providing more stable anticoagulation activity [11]. NOACs have few drug interactions and do not interact with food or alcohol, also resulting in a more stable anticoagulant intensity. Finally, NOACs do not require frequent laboratory monitoring. In contrast to mechanical valve thrombosis, where VKAs are needed to act against activation of the contact pathway [12], most intra-atrial thrombi develop using a pathophysiology through low flow, where NOACs have shown to be efficacious when one considers the results of large RCTs in AF or venous thromboembolism. However, the use of NOACs still remains contraindicated in specific groups, such as those with severe renal failure, mechanical prosthetic valves, in pregnant women, with active malignancy needing chemotherapy interacting with NOACs, or with antiphospholipid syndrome [13,14]. Parenteral anticoagulation may also be considered when there is no other option [6], but it is clearly less convenient than oral anticoagulation

for a therapy to be taken over several weeks.

In a retrospective study [15] involving 609 patients on NOACs (dabigatran, rivaroxaban, or apixaban), with a median anticoagulation time of 12 weeks, 17 patients (2.8%) had LA thrombus and 15 (2.5%) had dense spontaneous echo contrast detected by TEE, performed before catheter ablation of AF and flutter. A recent European survey showed a significant rate of use of TEE before cardioversion or AF ablation in 54 European centres, extending beyond AF guideline-suggested indications [16].

An LAA occlusion device may be used to prevent thromboembolism in patients with AF when they have an absolute contraindication for long-term use of oral anticoagulants (OAC; generally a history of severe bleeding with no modifiable cause). A possible complication has been described in recent years, which is thrombus formation on the device. This complication may not be uncommon in patients with AF treated by LAA occlusion (4–7% in recent large series), and when present, is associated with a higher rate of stroke and systemic embolism [17-19].

Antithrombotic management after LAA occlusion has not yet been evaluated in a randomized manner and is based on historical studies, at least including aspirin. Both OAC and antiplatelet therapy may be independently associated with a lower risk of device-related thrombus [17], indicating that a strategy of no antithrombotic treatment is not appropriate in patients treated with LAA occlusion. Antiplatelet therapy may be needed in this specific setting, because implantation of the device is associated with platelet activation until its endothelialization is properly achieved. It is unclear whether antiplatelet therapy is very useful in other patients with intra-atrial thrombus. Anticoagulation for weeks to months with a VKA or NOAC may lead to thrombus resolution in many cases, as may be seen for LAA thrombus. Therefore, anticoagulant therapy is recommended in all patients with device-associated thrombus regardless of symptoms, until thrombus resolution is confirmed by follow-up transoesophageal echocardiography [18] and/or computed tomography scan [20].

Many clinicians would be ready to manage left ventricular thrombus with a NOAC [21]. A common question is whether the preliminary and rather promising results when managing LA thrombus with NOACs also apply to patients with left ventricular thrombus. The picture is a little different because the pathophysiology may differ from that seen in AF patients, left ventricular thrombus most often being identified in the setting of acute myocardial infarction. While the Virchow triad may similarly be relevant for these patients, the level of evidence for the use of NOACs in this

context is even lower than that for intra-atrial thrombus [21,22]. The well demonstrated long-term clinical benefit of NOACs in AF [23] does not apply in the setting of acute coronary syndromes. Most recent European guidelines recommend that anticoagulation (not specifying whether this includes NOACs) should be administered for up to 6 months, guided by repeated imaging in post-infarct ventricular thrombosis [24].

So far, the specific benefit of NOACs on LA thrombus associated with AF has not been formally evaluated in adequately powered RCTs. Considering that the optimal type, dosage, and treatment duration of NOAC remain largely unknown in this setting, and in view of the current guidelines for the treatment of venous thromboembolism, it has also been suggested that loading doses of NOACs may sound logical for dissolving intra-cardiac thrombus [6,25]. A relevant design and adequate enrolment in a dedicated RCT in these patients is somewhat difficult to obtain, considering the many different clinical scenarios for the relatively few cases, in comparison to the various cardioversion RCTs, which were not fully powered to demonstrate efficacy on hard clinical endpoints such as stroke or systemic embolism. An ongoing open-label study is investigating the efficacy of edoxaban in patients with AF and atrial/LAA thrombosis (NCT03489395), and the RE-LATED AF trial will assess whether dabigatran results in faster complete LAA thrombus resolution compared with phenprocoumon (NCT02256683). These ongoing studies may provide new answers in the near future.

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