

Echocardiography in patients undergoing cardioversion for atrial fibrillation and inadequate anticoagulation: a step beyond towards maximum safety!

Paolo Colonna, Ilaria Dentamaro

Cardiology Department, Hospital Policlinico of Bari, Bari, Italy

Introduction The search for embolic sources in patients with atrial fibrillation (AF) undergoing electrical cardioversion (ECV) is fundamental as an alternative to 4 weeks of anticoagulation, but especially in patients with inadequate anticoagulation. In fact, the left atrial appendage (LAA) is the most common source of cardioembolic stroke in AF, where it represents the site of thrombus formation in more than 90% of cases.¹ Inadequate anticoagulation can occur in patients with difficulties in taking medications or in urgent cases (such as in impending myocardial ischemia, symptomatic hypotension, angina, or heart failure, where there is a rapid ventricular rate not responsive to pharmacological measurements and in patients with ventricular pre-excitation in the presence of rapid tachycardia or hemodynamic instability).²

In clinical practice, only half of the patients treated with vitamin K antagonists (VKAs) usually keep the therapeutic range of international normalized ratio for the precardioversion time of 3 weeks.³ Furthermore, when using non-vitamin K oral anticoagulants (NOACs), poor compliance or poor persistence of some patients can occur, as observed in the RE-LY study, where one-fifth of the patients stopped taking dabigatran after 2 years, despite the indication for continuous treatment.⁴ In these patients, it could be helpful to evaluate morphological and functional cardiac indicators of thromboembolic risk in order to make a decision to perform ECV. In patients on NOACs, a precardioversion transesophageal echocardiogram (TEE) should be performed if the therapy adherence is considered inadequate or if in doubt about the reliability of the patients.

In the current issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Zaprutko

et al⁵ also reported that LAA thrombus can be considered a surrogate endpoint for the risk of stroke. Yarmohammadi et al⁶ showed that patients with high and lower CHADS₂ scores, who had AF for more than 48 hours and were scheduled to undergo TEE before ECV, had a similar prevalence of LAA thrombus and stroke. They demonstrated that in the preprocedural risk assessment of these patients, the CHADS₂ scoring system is not reliable in predicting risk for LAA thrombus formation, especially in patients with low CHADS₂ scores, supporting the idea that a prior TEE is critical for an appropriate therapeutic decision.⁶ Moreover, the detection of spontaneous echo contrast (SEC), with its progressive grading from light to dense to sludge, represents a cardiac indicator of thromboembolic risk, and its presence can be considered as a supplementary factor prior to ECV, due to its association with left atrial (LA) thrombus, increased thromboembolic complications, and death. Bernhardt et al⁷ demonstrated this association in 128 patients with AF and dense SEC, performing serial, prospective TEE and cranial magnetic resonance imaging (MRI), and concluded that patients with dense SEC have a high likelihood of cerebral embolism and death, despite oral anticoagulation.

While adequate anticoagulation (both with VKAs or NOACs) is very effective in preventing the presence of LA thrombus and in treating LA thrombi in patients with nonvalvular AF, it does not affect red-cell aggregation in vitro or LA SEC.⁸ NOACs can be effective also for red-cell aggregation and SEC, as demonstrated by our previous study, in which attenuation of SEC occurred during therapy with dabigatran and not during well-controlled warfarin therapy.⁹ Therefore, it is fundamental to exclude these conditions with

Correspondence to:

Paolo Colonna, MD, FESC, Cardiology Department, Hospital Policlinico of Bari, Piazza G. Cesare, Bari 70124, Italy, phone: +39 080 5592424,

e-mail: colonna@tiscali.it

Received: June 14, 2017.

Accepted: June 14, 2017.

Published online: August 3, 2017.

Conflict of interests: PC is a coauthor of the European Society of Cardiology guidelines on atrial fibrillation (versions 2010 and 2012) and received honoraria and institutional funds for trials from Bayer, Boehringer, Pfizer, and Daiichi-Sankyo.

Pol Arch Intern Med. 2017; 127 (7-8): 468-470

doi:10.20452/pamw.4070

Copyright by Medycyna Praktyczna, Kraków 2017

TEE in order to have a safely guided ECV, especially in patients with inadequate anticoagulation, and where there is a fear of poor patient adherence to drug intake with NOACs.

Novel contributions in patients undergoing cardioversion for atrial fibrillation and inadequate anticoagulation: the search for maximum safety In their paper, Zaprutko et al⁵ evaluated the risk factors for LA SEC and LAA thrombus in patients with AF admitted to the hospital for urgent or elective ECV, including a large cohort of patients with inadequate anticoagulation prior to hospitalization. They showed that patients with AF, inadequately treated with anticoagulation therapy, are predisposed to thrombus formation in the LAA. Once thrombus is excluded, ECV is a safe procedure, and TEE before ECV should be performed in these patients in accordance with the guidelines. The authors analyzed clinical and echocardiographic variables in patients with LAA thrombus and SEC, and compared them with those in patients without any LA abnormalities on TEE. They found that the presence of the thrombus in the LAA did not depend on the mode of admission to the hospital, duration of arrhythmia, or the type of anticoagulation, but only on a history of myocardial infarction (odds ratio [OR], 3.92; 95% CI, 1.34–11.48; $P = 0.009$).

On the other hand, the presence of SEC in the LA identified patients with a higher risk of HF, of left ventricular ejection fraction lower than 40%, and of LA diameter exceeding 45 mm, but in the multivariate analysis, the SEC was significantly predictive only of the LA of more than 45 mm (OR, 3.08; 95% CI, 1.3–7.29). Furthermore, Zaprutko et al⁵ analyzed the relationship of LA SEC and LAA thrombus with the CHA₂DS₂-VASc score. In other papers, an increased CHA₂DS₂-VASc score was associated with higher detection rates of LAA thrombus and LA SEC as well as thromboembolic events.⁶ However, Zaprutko et al⁵ did not observe a relationship between the CHA₂DS₂-VASc score and the risk of LAA thrombus ($P = 0.08$) or SEC in the LA ($P = 0.53$), especially in patients with a CHA₂DS₂-VASc of less than 2, highlighting that in this case the anticoagulation therapy should be considered depending on the individual characteristics of the patients.

The study by Zaprutko et al⁵ has only a few limitations, mostly connected with the small sample size that made some parameters nonsignificant predictors of the presence of LAA thrombus. These parameters included the CHA₂DS₂-VASc score, LA dimensions, and left ventricular ejection fraction, all of which appear to be impaired in patients with LAA thrombi, but without significance.

Moreover, the LAA is usually very well depicted with 2-dimensional TEE, which is considered the gold standard for its assessment, with a high degree of sensitivity and a specificity ranging from 93% to 100% for the study of LAA anatomy and morphology, thrombi or sludge, dense SEC, and low peak flow velocity.¹⁰ One important

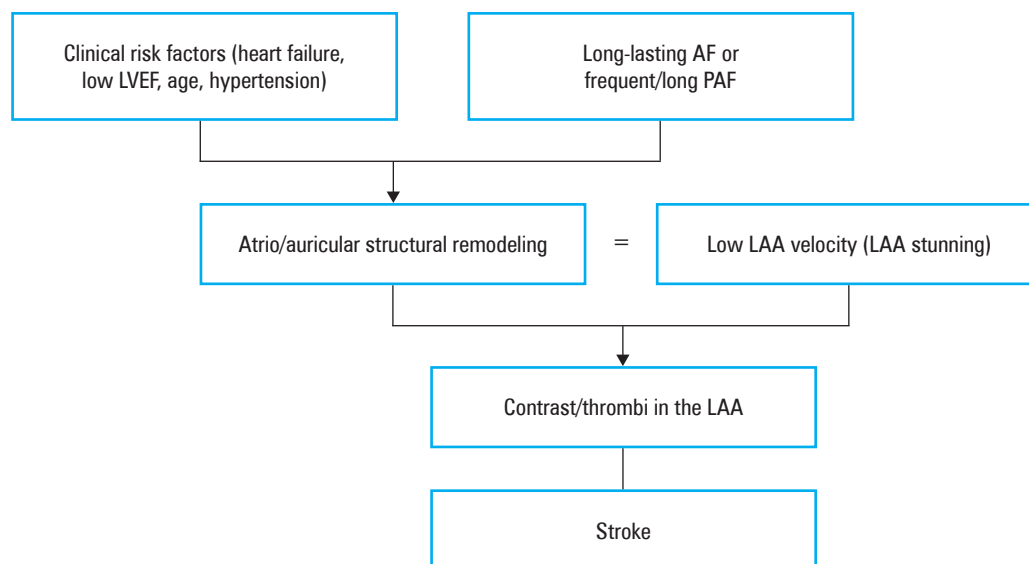
limitation of the study described by the authors is that the presence or absence of LAA thrombus was not confirmed by other “gold standard” imaging modalities, such as computed tomography or cardiac MRI, or by direct visual inspection of anatomic or surgical specimens. Transthoracic echocardiography almost never provides LAA images of the quality satisfactory enough to exclude LAA thrombosis; therefore, TEE is necessary to ensure the safety of ECV. However, a high rate of false positive results for LAA thrombus can be also reported with TEE, especially in the absence of a 3-dimensional evaluation that can reduce this limitation. In fact, the traditional bidimensional TEE visualizes only one plane at any given time, preventing a comprehensive examination of the LAA and making it difficult to differentiate a clot from pectinate muscles in some patients. This limitation may be overcome by real-time 3-dimensional transthoracic echocardiography, increasing the accuracy for the identification of the presence or absence of a thrombus and differentiating it from pectinate muscles, similarly to computed tomography or cardiac MRI.¹¹

In addition, a complete morphological and functional evaluation of the LA should be performed, including its shape, area, and volume, and the evaluation of the contractile function of the LA with the measurement of emptying velocity.¹² These parameters are considered to be indicators of the thromboembolic risk, and the lack of their evaluation could limit the reliability of the LA assessment.¹³

The final challenging aspect of the study is the evaluation of the presence of LA SEC and LAA thrombus in patients treated with different types of anticoagulant therapy, such as dual antithrombotic therapy (oral anticoagulant plus a single antiplatelet: aspirin or clopidogrel), triple antithrombotic therapy (oral anticoagulant, aspirin, and clopidogrel), single aspirin, single clopidogrel, or dual antiplatelet treatment (aspirin and clopidogrel), which could differently affect the LA thrombus formation and should be included in the primary evaluation of patients as well as in diagnostic and therapeutic decision making.

Future perspectives In the era of NOACs, with a higher efficacy in thromboembolism protection and a better safety in terms of major hemorrhages, the evaluation of the CHA₂DS₂-VASc score and other risk scores is even more important, but sometimes needs refinement (FIGURE 1). The paper by Zaprutko et al⁵ is important in that it shows how in inadequately anticoagulated patients undergoing ECV, the CHA₂DS₂-VASc score is insufficient to determine the risk of thrombus. Therefore, the addition of echocardiography is fundamental in selected groups of AF patients, where the decision to introduce warfarin or NOACs is debatable because of low embolic risk (CHA₂DS₂-VASc, 1–2) and high hemorrhagic risk (HAS-BLED ≥ 3). In these patients, the evaluation of AF etiology and LV function is the

FIGURE 1 Patho-physiological cascade
Abbreviations: AF, atrial fibrillation; LAA, left atrial appendage; PAF, paroxysmal atrial fibrillation



first echocardiographic step, indicative of an indirect sign of increased embolic risk. The second step is the precise description of the LA and LAA with the direct signs of LAA dysfunction on TEE. The presence of thrombi or of other direct signs of embolic risk (dense SEC, low emptying velocity on pulsed-wave Doppler ultrasound) indicates high embolic risk, which will increase in the presence of myocardial infarction or heart failure. Better knowledge of AF, thrombus pathophysiology, and LA function, with the use of echocardiography, allows making reasonable decisions about anticoagulation and facilitates diagnosis when fast ECV is necessary.

11 Dentamaro I, Vestito D, Michelotto E, et al. Evaluation of left atrial appendage function and thrombi in patients with atrial fibrillation: from transthoracic to real time 3D transesophageal echocardiography. *Int J Cardiovasc Imaging*. 2017; 33: 491-498.

12 de Luca I, Colonna P, Sorino M, et al. New monodimensional transthoracic echocardiographic sign of left atrial appendage function. *J Am Soc Echocardiogr*. 2007; 20: 324-332.

13 Sorino M, Colonna P, De Luca L, et al. Post cardioversion transesophageal echocardiography (POSTEC) strategy with the use of Enoxaparin for brief anticoagulation in atrial fibrillation patients: the multicenter POSTEC trial (a pilot study). *J Cardiovasc Med*. 2007; 8: 1034-1042.

REFERENCES

- 1 Bouzas-Mosquera A, Broullón FJ, Álvarez-García N, et al. Left atrial size and risk for all-cause mortality and ischemic stroke. *CMAJ*. 2011; 183: 657-664.
- 2 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016; 37: 2893-2962.
- 3 Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *Am Heart J*. 2015; 170: 141-148.
- 4 Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (rely-able) study. *Circulation*. 2013; 128: 237-224.
- 5 Zaprutko J, Baszko A, Michalak M, et al. Safety of transesophageal echocardiography-guided electrical cardioversion in patients with atrial fibrillation and inadequate anticoagulation. *Pol Arch Intern Med*. 2017; 127: 524-531.
- 6 Yarmohammadi H, Varr BC, Puwanant S, et al. Role of CHADS2 score in evaluation of thromboembolic risk and mortality in patients with atrial fibrillation undergoing direct current cardioversion (from the ACUTE Trial Substudy). *Am J Cardiol*. 2012; 110: 222-226.
- 7 Bernhardt P, Schmidt H, Hammerstingl C, et al. Patients with atrial fibrillation and dense spontaneous echo contrast at high risk a prospective and serial follow-up over 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *JACC*. 2005; 45: 1807-1812.
- 8 Ito T, Suwa M, Nakamura T, et al. Influence of warfarin therapy on left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *Am J Cardiol*. 1999; 84: 857-859.
- 9 Vestito D, De Santis D, Colonna P. Three-dimensional transesophageal echocardiography demonstration of left atrial appendage echocontrast regression after 6 months therapy with dabigatran and not with warfarin. *J Cardiovasc Echography*. 2016; 26: 52-55.
- 10 Latcu DG, Rinaldi JP, Saoudi N. Real-time three-dimensional transesophageal echocardiography for diagnosis of left atrial appendage thrombus. *Eur J Echocardiogr*. 2009; 10: 711-712.