



Review

Diagnosis and Management of Left Atrium Appendage Thrombosis in Atrial Fibrillation Patients Undergoing Cardioversion

Enrico Melillo ^{1,*}, Giuseppe Palmiero ¹, Adele Ferro ², Paola Elvira Mocavero ³, Vittorio Monda ¹ and Luigi Ascione ¹

¹ Department of Cardiology, AO dei Colli, Monaldi Hospital, 80131 Naples, Italy

² Institute of Biostructure and Bioimaging, National Council Research, 80131 Naples, Italy

³ Anesthesiology and Intensive Care Unit, AO dei Colli, Monaldi Hospital, 80131 Naples, Italy

* Correspondence: doc.emelillo88@gmail.com; Tel.: +39-08-1706-2302

Received: 25 June 2019; Accepted: 19 August 2019; Published: 21 August 2019



Abstract: Atrial fibrillation is the most common cardiac arrhythmia and is associated with an increased risk of stroke and thromboembolic complications. A rhythm control strategy with both electrical and pharmacological cardioversion is recommended for patients with symptomatic atrial fibrillation. Anticoagulant therapy for 3–4 weeks prior to cardioversion is recommended in order to avoid thromboembolic events deriving from restoring sinus rhythm. Transesophageal echocardiography has a pivotal role in this setting, excluding the presence of left atrial appendage thrombus before cardioversion. The aim of this review is to discuss the epidemiology and risk factors for left atrial appendage thrombosis, the role of echocardiography in the decision making before cardioversion, and the efficacy of different anticoagulant regimens on the detection and treatment of left atrial appendage thrombosis.

Keywords: atrial fibrillation; cardioversion; oral anticoagulation therapy; left atrial appendage thrombosis; transesophageal echocardiography

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a prevalence of 0.4% in the general population and 9% in octogenarian patients [1]. Patients with AF have a higher risk of cardiovascular complications, including a 3–5-fold increase of stroke [2]. A 4–5 fold risk of systemic embolism (SE) [3] and a higher risk of heart failure (HF) development [4]. Without prior adequate anticoagulation, cardioversion (CV) (both electric and pharmacological) in patients with AF is associated with a non-negligible risk of thromboembolic events [5]. Consequently, for patients with AF >48 h onset, the current guidelines recommend anticoagulant therapy for at least three weeks before and four weeks after CV [6]. The transesophageal echocardiogram (TOE) is a diagnostic method that allows a detailed evaluation of the anatomy and function of the left atrial appendage (LAA), and is considered the gold standard for identifying or excluding left atrium (LA) and LAA thrombosis [6]. Vitamin K antagonists (VKAs) have traditionally been considered the gold standard for thromboembolic prophylaxis before CV; however, novel oral anticoagulants (NOACs) have also been studied, and are increasingly employed in this setting [7–9]. The aim of this review is to discuss the risk factors and diagnostic modalities of LAA thrombosis in AF patients undergoing CV, and to provide a summary and update of the therapeutic strategies to prevent and resolve LAA thrombosis.

2. Risk Factors of Left Atrial Appendage Thrombosis

LAA is the most prominent site of LA thrombus formation, with more than 90% of thrombi generating within this anatomical structure [10]. Extra-appendage thrombosis is a very rare finding in non-valvular AF and, when present, an LAA thrombus is usually concomitant [11]. The CHA₂DS₂-VASc score incorporates the more common stroke risk factors seen in everyday clinical practice, and is recommended to guide anticoagulant therapy in AF patients. CHA₂DS₂-VASc and older CHADS₂ scoring systems are also good predictors of LAA thrombosis. CHA₂DS₂-VASc showed a higher sensibility and specificity for LAA thrombus detection, and severe impairment of left ventricle systolic function is a powerful predictor of LAA thrombosis [12–14]. Moreover, the addition of the AF type (persistent AF) and renal function to the CHA₂DS₂-VASc score may better stratify thromboembolic risk and could identify patients who do not need preprocedural TOE [15]. In AF patients with low thromboembolic risk, the CHA₂DS₂-VASc score seems more able to identify low-risk individuals with a low probability of LAA thrombus, as seen in two retrospective studies totaling 1100 AF patients where no LAA thrombi were identified in individuals with a CHA₂DS₂-VASc score <2 [16,17]. Conversely, a low CHADS₂ score is less reliable in predicting the risk of LAA thrombus formation [18].

Moreover, the addition of biomarkers such as brain natriuretic peptide can improve the risk stratification of CHADS₂ and CHA₂DS₂-VASc scores for LAA thrombus [19,20].

3. The Role of Echocardiography before Cardioversion

3.1. Transthoracic Echocardiography

Transthoracic echocardiography (TTE) should be performed for the clinical evaluation of every AF patient. TTE provides a comprehensive evaluation of cardiac anatomy and function that can help to define the type of AF and to identify patients with high risk of LAA thrombosis. Firstly, echocardiographic assessment is necessary to diagnose valvular AF, defined by the presence of moderate–severe mitral stenosis or a prosthetic valve, which is necessarily treated with VKAs anticoagulant therapy [6]. TTE provides an overall assessment of left ventricle ejection fraction (LVEF), a risk marker of both stroke and LAA thrombus presence before CV [21]. An LVEF < 40% is considered an equivalent of the congestive HF criterion in the CHA₂DS₂-VASc score, while a normal LVEF has been associated with a low prevalence of LAA thrombosis in AF patients undergoing TOE [22]. Evaluation of LA dimension is fundamental in assessing risk of LAA thrombosis and the probability of successful rhythm control [23]. The measurement of antero-posterior LA diameter has been traditionally considered the gold standard for LA dimension assessment. However, growing evidence suggests that the LA volume index (LAVI) is a more powerful predictor of LAA thrombus. [22]. Furthermore, a combination of LVEF-to-LAVI ratio <1.5 showed a 100% sensitivity in predicting the presence of LAA thrombus, therefore identifying a low-risk population before CV [24].

TTE provides markers to predict the probability of successful rhythm control before CV. LAVI, LVEF, diastolic function, E/è wave ratio, and LV hypertrophy can influence the outcome of rhythm control strategy [25,26]. The HATCH score (which stands for hypertension, age 75 years, thromboembolic event, pulmonary disease, and HF) summarizes the main markers affecting the likelihood of a successful CV [27].

The assessment of LA function with 2D speckle tracking echocardiography (STE) is a promising tool in the clinical evaluation of AF patients. Normal LA strain analysis with STE has three phases: active filling phase (reservoir), passive emptying phase (conduit), and booster pump phase (pump), which corresponds to LA contraction at the end of the ventricular diastole. In AF patients, the booster pump phase is missing, and the most reliable parameter is the peak systolic reservoir strain. STE deformation analysis is highly correlated with the amount of LA interstitial fibrosis and remodeling process occurring in AF patients [28]. A reduced peak positive strain has been associated with lower LAA emptying velocities, with an LA prothrombotic state, and with higher incidence of LAA thrombosis [29,30].

3.2. Transesophageal Echocardiography and Intracardiac Echocardiography

TOE is considered the gold standard modality for diagnosis of LAA thrombi with a sensitivity and specificity of 95%–100% [31]. Current guidelines recommend TOE as an alternative to periprocedural anticoagulation in patients with >48 h AF duration or when the exact duration and onset of AF cannot be determined [6]. Moreover, in patients where thrombosis is identified, a repeat TOE after 3–4 weeks of anticoagulation should be considered before CV [6]. Modern multiplane TOE enables a visual assessment of LAA thrombi (Figure 1) or other potential intracardiac sources of embolism. TOE allows visual diagnosis of spontaneous echo contrast (SEC), also called “smoke” (Figure 2B), and “sludge” (Figure 2A), a dense and marked SEC, which is a precursor of thrombus formation and has a greater prognostic significance than smoke alone [32]. LAA mechanical function can be assessed from TOE with pulsed wave Doppler sample volume placed 1 cm below LAA ostium. LAA emptying velocities <20 cm/s are associated with a higher prevalence of SEC and LAA thrombosis [33] (Figure 2B). A combined use of color and pulsed-wave Doppler with contrast echocardiography can provide incremental information in aiding the diagnosis of LAA thrombosis in patients with doubtful diagnosis [34].

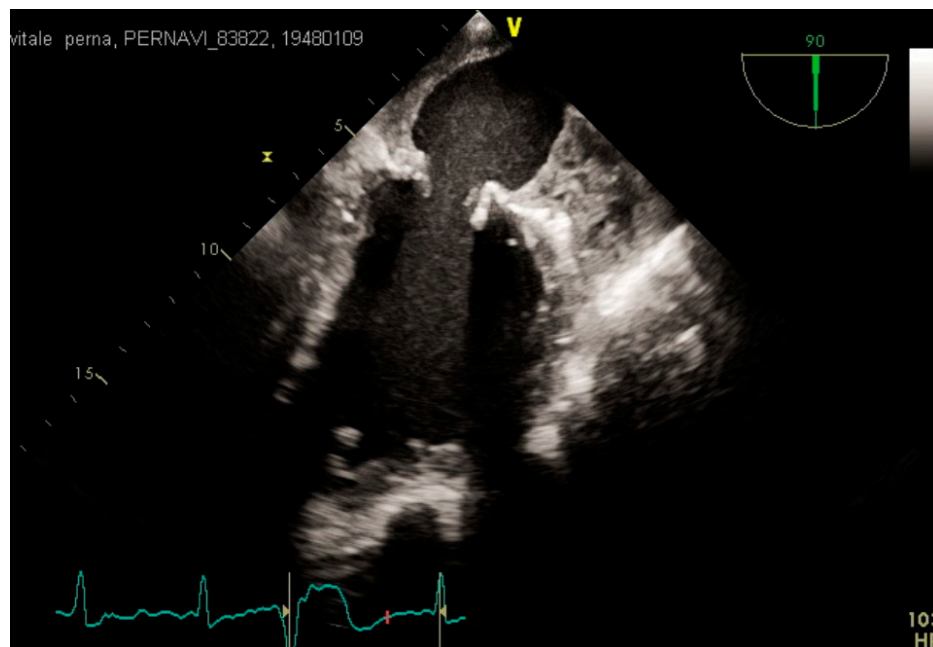


Figure 1. Transesophageal echocardiogram (TOE) intercommissural view showing massive left atrium (LA) and left atrial appendage (LAA) thrombosis.

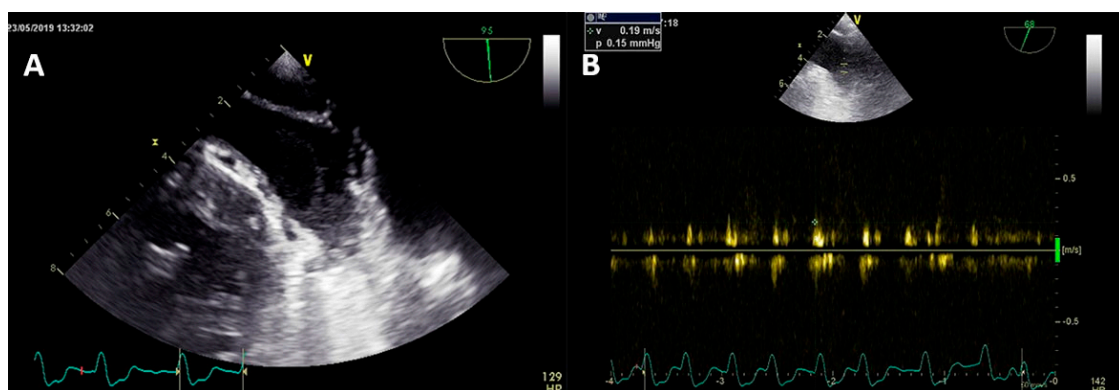


Figure 2. Detection of sludge in LAA with swirling effect (A) and associated low LAA emptying velocities (B).

However, despite the high sensitivity for thrombus detection, there are some potential limitations of the traditional bidimensional TOE. TOE may misdiagnose thrombi <2 mm, which have high embolic potential, especially in the setting of complex multilobed LAA anatomy [35]. Moreover, the LAA has a complex and highly variable three-dimensional morphology, which can render its assessment difficult using 2D TOE alone. In particular, the presence of pectinate muscles, multilobed appendage morphology, SEC, or acoustic shadowing from the Coumadin ridge might be misinterpreted as thrombi, and could prevent the accurate evaluation of the LAA with traditional 2D imaging [36]. 3D TOE improves the evaluation of LAA anatomy, overcoming some limitations associated with 2D imaging. 3D TOE enables a multiplanar reconstruction that provides a more extensive evaluation of the LAA (especially of complex multilobe morphologies), and a better depiction of the surrounding anatomical landmarks [37] (Figure 3). There is a lack of evidence regarding the sensitivity and specificity of 3D TOE for detecting LAA thrombosis. However, a recent report suggests that 3D TOE should be suggested when the diagnosis of LAA thrombosis remains equivocal after a detailed 2D analysis [36]. Moreover, with the widespread diffusion of LAA percutaneous closure techniques and increasing operator experience in 3D imaging, it is reasonable that 3D TOE will have a growing role in the diagnosis of LAA thrombosis.

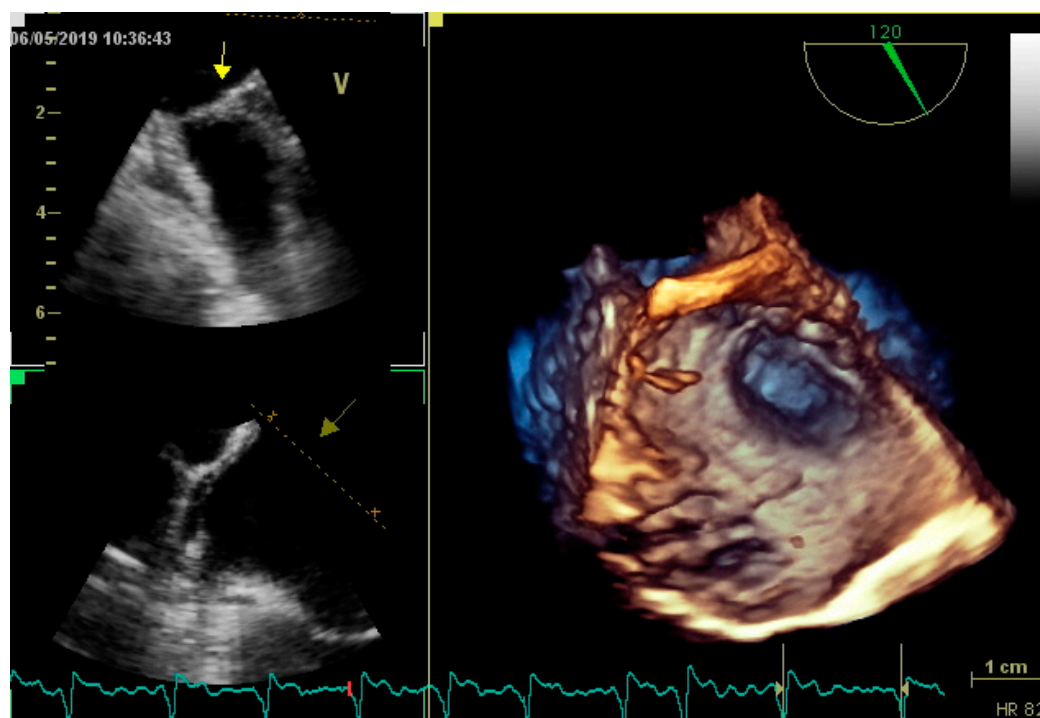


Figure 3. A three-dimensional TOE imaging of LAA.

Finally, intracardiac echocardiography (ICE) is an alternative imaging method of the LAA, usually indicated when TOE is contraindicated or not obtainable. ICE is performed with an 8–10 Fr catheter introduced through femoral venous access and advanced in right heart chambers under fluoroscopic guidance [38]. In the absence of interatrial transeptal crossing, the LAA can be displayed indirectly through the right ventricle outflow tract and the pulmonary artery, considering their close anatomical relationship [39]. Although ICE is less sensitive than TOE for thrombus detection [40], it can serve as a complementary method—especially when equivocal TOE findings require further evaluation. However, considering its invasive nature, in practice ICE is mainly performed in the catheterization laboratory during planned interventional cardiac procedures and when TOE is contraindicated.

4. Prevention and Treatment of Left Atrial Appendage Thrombosis

CV is associated with an increased risk of thromboembolic events and strokes. For patients with AF >48 h onset, current guidelines recommend anticoagulant therapy for at least three weeks before and four weeks after CV [6]. The reason for three weeks of anticoagulation before electrical CV derives from a study suggesting that at least 14 days are needed for fibroblastic infiltration and organization of an LAA thrombus [41]. The four weeks of anticoagulation after CV are due to postprocedural LA stunning, with marked impairment of Doppler-derived indexes of LA contraction that contribute to a higher risk of thromboembolic stroke [5,42].

VKAs are considered the gold standard for thromboembolic prophylaxis before CV, and are the only recommended treatment in patients with valvular AF [6]. Previous studies suggest that the incidence of LA/LAA thrombosis under treatment with VKAs ranges between 0.6% and 7%, depending on population study and sample size [43–45]. The narrow therapeutic interval and difficulties in keeping a target time in therapeutic range are considered the main limitations of VKA therapy.

NOACs are safe and effective alternatives to VKA therapy [46–49], and are currently considered as first-line therapy for long-term stroke prevention in patients with nonvalvular AF [6]. The overall safety and efficacy profile of NOACs have been confirmed in different clinical scenarios [50–58]. The clinical performance of NOACs in the setting of acute and elective CV has been addressed by three prospective randomized trials. In the X-Vert trial, 1504 patients with AF of either >48 h or unknown duration undergoing CV were randomized to once-daily rivaroxaban or VKA [7]. The composite endpoint of stroke or systemic embolism after CV occurred in 1.02% of patients on VKAs and in 0.51% of patients on rivaroxaban. More recently, the ENSURE-AF trial randomized 2199 patients with AF >48 h and <1 year duration undergoing electrical cardioversion to 60 mg edoxaban once daily or warfarin with enoxaparin bridging [8]. The primary efficacy composite endpoint of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality at 28 days post CV occurred in 1.0% of patients of both arms. The EMANATE trial randomized 1500 patients with AF of ≤48 h onset to apixaban or heparin/VKA [9]. The trial showed a significant reduction with apixaban in strokes (0% vs. 0.8%) and in major bleeding (0.4% vs. 0.8%) at 30 days compared to warfarin. The favorable clinical profile of NOACs in patients undergoing CV has also been confirmed in a recent metanalysis [59,60] and in real-world studies [61–66].

Probably as a result of this evidence, a recent multicentric European registry addressing NOAC strategies before CV showed a trend towards an increasing use of NOACs and a significant decrease of VKA use [67]. However, in this registry 68.5% of patients received VKA anticoagulant therapy before CV and clinicians appeared to hesitate to embrace NOAC usage before CV [67].

In a real-world clinical scenario, the average time to CV was shorter with NOACs compared to warfarin [62]. Moreover, a budget impact analysis showed that the potential use of an early rivaroxaban strategy before direct-current CV could lead to a significant saving of costs related to procedure [68]. Therefore, considering these positive points and the effective clinical profile versus warfarin, it is reasonable that the use of the NOAC anticoagulation strategy before CV could increase in coming years.

Although randomized trials have addressed the efficacy and clinical profile of NOACs versus warfarin before CV, the prevalence of LA/LAA thrombus after adequate anticoagulation with NOACs remains a relatively unaddressed issue. In the X-Vert study, a relatively high occurrence of LAA thrombi (18.2%) was observed in the 33 patients enrolled in the trial who underwent TOE before elective CV [7]. However, only about 10% of patients scheduled for elective CV in the X-Vert trial underwent TOE, and these data could explain the high percentage of LAA thrombosis. In the ENSURE-AF trial, 47 patients (8%) in the edoxaban arm and 42 patients (7.1%) in the enoxaparin-warfarin arm had LAA thrombosis on pre-CV TOE [8]. In the EMANATE trial, LA/LAA thrombus was detected in 61 patients (4%), 30 in the apixaban group, and 31 in the heparin/VKA group, in over 829 patients who underwent TOE before CV [9].

There is a paucity of data on the prevalence of LAA thrombosis on NOAC therapy before CV in a real-life setting. A multicenter real-world study performed in AF patients undergoing TOE 12 h

before CV or catheter ablation reported LAA thrombus in 3.6% of patients (15/414) with no significant difference between dabigatran, rivaroxaban, and apixaban [69]. Another recent real-world study showed LAA thrombosis in 7/127 patients (5.5%) and SEC in 24/127 (18.9%) [70].

Therefore, these data firstly suggest that LAA thrombosis is not a negligible event despite adequate anticoagulation, and that—although not universally accepted—a TOE-guided CV strategy is mandatory in order to reduce the burden of thromboembolic periprocedural events and to reduce bleeding events [71].

Once an LAA thrombus is identified, effective anticoagulation is recommended for at least three weeks or until LAA thrombus resolution is detected on follow-up TOE [6]. In this setting, VKA therapy for four weeks with repeat TOE showed resolution of thrombi in 80%–89% patients who were not previously anticoagulated [72,73]. If LAA thrombus occurs despite therapeutic anticoagulation, different strategies can be pursued, including switching to NOACs. Data are lacking on LAA resolution after NOACs therapy, and principally comprise case reports, where NOACs were initiated after failure of VKAs therapy or low time in therapeutic range [74–76]. The X-TRA multicenter prospective trial explored the use of rivaroxaban for the treatment of firstly-diagnosed LAA thrombus in 53 patients with available baseline and follow-up TOE [77]. About 75% of the patients had no prior anticoagulant therapy, while approximately one-quarter were treated with subtherapeutic VKA therapy. After six weeks of treatment, repeat TOE found a resolution of LAA thrombi in 41.5% of patients, 19% had LAA thrombi reduced in size, while 17% were unchanged and 22.5% had an increase in thrombi size [77].

In a recent retrospective study, among the 1485 patients with AF undergoing TOE, LAA thrombus or sludge was detected in 117 patients (7.8%) [78]. Of these, 39 (33%) were prescribed an NOAC, with rivaroxaban being the most frequently prescribed (54%). On repeat TOE, LAA thrombus resolution was seen in 37 patients (58.7%) with higher resolution rates, although not statistically significant, with NOAC therapy. A recent report on TOE showed 4.7% of LA/LAA thrombosis in 864 AF patients [79]. Follow-up TOE was performed in 22 patients, and 19 of them had LA/LAA thrombus resolution. In this real-world study, the preferred anticoagulant strategy was an uptitration of NOAC dosages and keeping higher INR values for warfarin therapy. However, a reduced NOAC dosage was most frequently associated with LA/LAA thrombi detection [79].

In conclusion, there is still a lack of solid evidence on the efficacy and safety of NOACs in LAA thrombus resolution. Current ongoing randomized trials comparing NOACs with VKAs in LA/LAA thrombosis resolution (rivaroxaban NCT03792152; dabigatran NCT02256683) will provide further evidence in this clinical scenario.

5. Conclusions

- The incidence of LAA thrombosis in AF patients undergoing CV is not a negligible event despite adequate anticoagulant therapy.
- A TOE-guided CV is a mandatory strategy in order to reduce the burden of periprocedural thromboembolic events.
- Although VKAs have been historically considered the cornerstone anticoagulant therapy before CV, growing evidence show that NOACs are safe and effective alternatives in this setting.
- Further and extended data are needed to assess the efficacy and safety profile of NOACs for the treatment of LAA thrombosis.

Author Contributions: E.M. and G.P. designed the paper structure; E.M., G.P., A.F., and P.E.M. performed the literature review; E.M. wrote the paper; V.M. and L.A. were responsible for final supervision and approval of the paper.

Funding: This research was not funded.

Acknowledgments: None to declare.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Feinberg, W.M.; Blackshear, J.L.; Laupacis, A.; Kronmal, R.; Hart, R.G. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch. Intern. Med.* **1995**, *155*, 469–473. [[CrossRef](#)] [[PubMed](#)]
2. Wolf, P.A.; Abbott, R.D.; Kannel, W.B. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* **1991**, *22*, 983–988. [[CrossRef](#)] [[PubMed](#)]
3. Frost, L.; Engholm, G.; Johnsen, S.; Moller, H.; Henneberg, E.W.; Husted, S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch. Intern. Med.* **2001**, *161*, 272–276. [[CrossRef](#)] [[PubMed](#)]
4. Wang, T.J.; Larson, M.G.; Levy, D.; Vasan, R.S.; Leip, E.P.; Wolf, P.A.; D'Agostino, R.B.; Murabito, J.M.; Kannel, W.B.; Benjamin, E.J. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation* **2003**, *107*, 2920–2925. [[CrossRef](#)] [[PubMed](#)]
5. Airaksinen, K.E.; Gronberg, T.; Nuotio, I.; Nikkinen, M.; Ylitalo, A.; Biancari, F.; Hartikainen, J.E. Thromboembolic complications after cardioversion of acute atrial fibrillation: The FinCV (Finnish CardioVersion) study. *J. Am. Coll. Cardiol.* **2013**, *62*, 1187–1192. [[CrossRef](#)] [[PubMed](#)]
6. Kirchhof, P.; Benussi, S.; Kotecha, D.; Ahlsson, A.; Atar, D.; Casadei, B.; Castella, M.; Diener, H.C.; Heidbuchel, H.; Hendriks, J.; et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* **2016**, *18*, 1609–1678. [[CrossRef](#)]
7. Cappato, R.; Ezekowitz, M.D.; Klein, A.L.; Camm, A.J.; Ma, C.S.; Le Heuzey, J.Y.; Talajic, M.; Scanavacca, M.; Vardas, P.E.; Kirchhof, P.; et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur. Heart J.* **2014**, *35*, 3346–3355. [[CrossRef](#)]
8. Goette, A.; Merino, J.L.; Ezekowitz, M.D.; Zamoryakhin, D.; Melino, M.; Jin, J.; Mercuri, M.F.; Grosso, M.A.; Fernandez, V.; Al-Saady, N.; et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial. *Lancet* **2016**, *388*, 1995–2003. [[CrossRef](#)]
9. Ezekowitz, M.D.; Pollack, C.V., Jr.; Halperin, J.L.; England, R.D.; VanPelt Nguyen, S.; Spahr, J.; Sudworth, M.; Cater, N.B.; Breazna, A.; Oldgren, J.; et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: The EMANATE trial. *Eur. Heart J.* **2018**, *39*, 2959–2971. [[CrossRef](#)]
10. Schotten, U.; Verheule, S.; Kirchhof, P.; Goette, A. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. *Physiol. Rev.* **2011**, *91*, 265–325. [[CrossRef](#)]
11. Cresti, A.; Garcia-Fernández, M.A.; Sievert, H.; Mazzone, P.; Baratta, P.; Solari, M.; Geyer, A.; De Sensi, F.; Limbruno, U. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: A large Transeophageal Echo study. *EuroIntervention* **2019**, *15*, e225–e230. [[CrossRef](#)]
12. Yarmohammadi, H.; Klosterman, T.; Grewal, G.; Alraies, M.C.; Varr, B.C.; Lindsay, B.; Zurick, A.O.; Shrestha, K.; Tang, W.H.; Bhargava, M.; et al. Efficacy of the CHADS₂ scoring system to assess left atrial thrombogenic milieu risk before cardioversion of non-valvular atrial fibrillation. *Am. J. Cardiol.* **2013**, *112*, 678–683. [[CrossRef](#)] [[PubMed](#)]
13. Zylla, M.; Pohlmeier, M.; Hess, A.; Mereles, D.; Kieser, M.; Bruckner, T.; Scholz, E.; Zitron, E.; Schweizer, P.A.; Katus, H.A.; et al. Prevalence of intracardiac thrombi under phenprocoumon, direct oral anticoagulants (dabigatran and rivaroxaban), and bridging therapy in patients with atrial fibrillation and flutter. *Am. J. Cardiol.* **2015**, *115*, 635–640. [[CrossRef](#)]
14. Willens, H.J.; Gomez-Marin, O.; Nelson, K.; DeNicco, A.; Moscucci, M. Correlation of CHADS₂ and CHA₂DS₂-VASc scores with transesophageal echocardiography risk factors for thromboembolism in a multiethnic United States population with nonvalvular atrial fibrillation. *J. Am. Soc. Echocardiogr.* **2013**, *26*, 175–184. [[CrossRef](#)]
15. Sikorska, A.; Baran, J.; Pilichowska-Paszkiel, E.; Sikora-Frac, M.; Kryński, T.; Piotrowski, R.; Stec, S.; Zaborska, B.; Kułakowski, P. Risk of left atrial appendage thrombus in patients scheduled for ablation for atrial fibrillation: Beyond the CHA₂DS₂VASc score. *Pol. Arch. Med. Wewnętrznej* **2015**, *125*, 921–928. [[CrossRef](#)]

16. Uz, O.; Atalay, M.; Dogan, M.; Isilak, Z.; Yalcin, M.; Uzun, M.; Kardesoglu, E.; Cebeci, B.S. The CHA2DS2-VASc score as a predictor of left atrial thrombus in patients with non-valvular atrial fibrillation. *Med. Princ. Pract.* **2014**, *23*, 234–238. [[CrossRef](#)] [[PubMed](#)]
17. Tang, R.B.; Dong, J.Z.; Liu, X.P.; Long, D.Y.; Yu, R.H.; Du, X.; Liu, X.H.; Ma, C.S. Is CHA2DS2-VASc score a predictor of left atrial thrombus in patients with paroxysmal atrial fibrillation? *Thromb. Haemost.* **2011**, *105*, 1107–1109. [[CrossRef](#)] [[PubMed](#)]
18. Yarmohammadi, H.; Varr, B.C.; Puwanant, S.; Lieber, E.; Williams, S.J.; Klostermann, T.; Jasper, S.E.; Whitman, C.; Klein, A.L. 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. [[CrossRef](#)] [[PubMed](#)]
19. Ochiuni, Y.; Kagawa, E.; Kato, M.; Sasaki, S.; Nakano, Y.; Itakura, K.; Takiguchi, Y.; Ikeda, S.; Dote, K. Usefulness of brain natriuretic peptide for predicting left atrial appendage thrombus in patients with unanticoagulated nonvalvular persistent atrial fibrillation. *J. Arrhythmia* **2015**, *31*, 307–312. [[CrossRef](#)]
20. Habara, S.; Dote, K.; Kato, M.; Sasaki, S.; Goto, K.; Takemoto, H.; Hasegawa, D.; Matsuda, O. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *Eur. Heart J.* **2007**, *28*, 2217–2222. [[CrossRef](#)] [[PubMed](#)]
21. Lip, G.Y.; Nieuwlaat, R.; Pisters, R.; Lane, D.A.; Crijns, H.J. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest* **2010**, *137*, 263–272. [[CrossRef](#)] [[PubMed](#)]
22. Ayirala, S.; Kumar, S.; O’Sullivan, D.M.; Silverman, D.I. Echocardiographic predictors of left atrial appendage thrombus formation. *J. Am. Soc. Echocardiogr.* **2011**, *24*, 499–505. [[CrossRef](#)] [[PubMed](#)]
23. Marchese, P.; Bursi, F.; Delle Donne, G.; Malavasi, V.; Casali, E.; Barbieri, A.; Melandri, F.; Modena, M.G. Indexed left atrial volume predicts the recurrence of non-valvular atrial fibrillation after successful cardioversion. *Eur. J. Echocardiogr.* **2011**, *12*, 214–221. [[CrossRef](#)] [[PubMed](#)]
24. Doukky, R.; Khandelwal, A.; Garcia-Sayan, E.; Gage, H. External validation of a novel transthoracic echocardiographic tool in predicting left atrial appendage thrombus formation in patients with nonvalvular atrial fibrillation. *Eur. Heart J. Cardiovasc. Imaging* **2013**, *14*, 876–881. [[CrossRef](#)] [[PubMed](#)]
25. Donal, E.; Lip, G.Y.; Galderisi, M.; Goette, A.; Shah, D.; Marwan, M.; Lederlin, M.; Mondillo, S.; Edvardsen, T.; Sitges, M.; et al. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur. Heart J. Cardiovasc. Imaging* **2016**, *17*, 355–383. [[CrossRef](#)] [[PubMed](#)]
26. Fornengo, C.; Antolini, M.; Frea, S.; Gallo, C.; Grosso Marra, W.; Morello, M.; Gaita, F. Prediction of atrial fibrillation recurrence after cardioversion in patients with left-atrial dilation. *Eur. Heart J. Cardiovasc. Imaging* **2015**, *16*, 335–341. [[CrossRef](#)]
27. de Vos, C.B.; Pisters, R.; Nieuwlaat, R.; Prins, M.H.; Tieleman, R.G.; Coelen, R.J.S.; van den Heijkant, A.C.; Allessie, M.A.; Crijns, H.J. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J. Am. Coll. Cardiol.* **2010**, *55*, 725–731. [[CrossRef](#)]
28. Cameli, M.; Mandoli, G.E.; Loiacono, F.; Sparla, S.; Iardino, E.; Mondillo, S. Left atrial strain: A useful index in atrial fibrillation. *Int. J. Card.* **2016**, *220*, 208–213. [[CrossRef](#)]
29. Cameli, M.; Lunghetti, S.; Mandoli, G.E.; Righini, F.M.; Lisi, M.; Curci, V.; Di Tommaso, C.; Solari, M.; Nistor, D.; Gismondi, A.; et al. Left Atrial Strain Predicts Pro-Thrombotic State in Patients with non-valvular Atrial Fibrillation. *J. Atr. Fibrillation* **2017**, *10*, 1641. [[CrossRef](#)]
30. Costa, C.; Alujas, T.G.; Valente, F.; Aranda, C.; Rodríguez-Palomares, J.; Gutierrez, L.; Maldonado, G.; Galian, L.; Teixidó, G.; Evangelista, A. Left atrial strain: A new predictor of thrombotic risk and successful electrical cardioversion. *Echo Research and practice.* *Echo Res. Pract.* **2016**, *3*, 45–52. [[CrossRef](#)]
31. Manning, W.J.; Weintraub, R.M.; Waksmonski, C.A.; Haering, J.M.; Rooney, P.S.; Maslow, A.D.; Johnson, R.G.; Douglas, P.S. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann. Intern. Med.* **1995**, *123*, 817–822. [[CrossRef](#)] [[PubMed](#)]
32. Troughton, R.W.; Asher, C.R.; Klein, A.L. The role of echocardiography in atrial fibrillation and cardioversion. *Heart* **2003**, *89*, 1447–1454. [[CrossRef](#)] [[PubMed](#)]
33. Black, I.W. Spontaneous echo contrast: Where there’s smoke there’s fire. *Echocardiography* **2000**, *17*, 373–382. [[CrossRef](#)] [[PubMed](#)]

34. Ruiz-Arango, A.; Landolfo, C. A novel approach to the diagnosis of left atrial appendage thrombus using contrast echocardiography and power Doppler imaging. *Eur. J. Echocardiogr.* **2008**, *9*, 329–333. [[CrossRef](#)] [[PubMed](#)]
35. Veinot, J.P.; Harrity, P.J.; Gentile, F.; Khandheria, B.K.; Bailey, K.R.; Eickholt, J.T.; Seward, J.B.; Tajik, A.J.; Edwards, W.D. Anatomy of the normal left atrial appendage: A quantitative study of age-related changes in 500 autopsy hearts—implications for echocardiographic examination. *Circulation* **1997**, *96*, 3112–3115. [[CrossRef](#)] [[PubMed](#)]
36. Squara, F.; Bres, M.; Baudouy, D.; Schouver, E.D.; Mocerri, P.; Ferrari, E. Transesophageal echocardiography for the assessment of left atrial appendage thrombus: Study of the additional value of systematic real time 3D imaging after regular 2D evaluation. *Echocardiography* **2018**, *35*, 474–480. [[CrossRef](#)] [[PubMed](#)]
37. Nakajima, H.; Seo, Y.; Ishizu, T.; Yamamoto, M.; Machino, T.; Harimura, Y.; Kawamura, R.; Sekiguchi, Y.; Tada, H.; Aonuma, K. Analysis of the left atrial appendage by three-dimensional transesophageal echocardiography. *Am. J. Cardiol.* **2010**, *106*, 885–892. [[CrossRef](#)] [[PubMed](#)]
38. Basman, C.; Parmar, Y.J.; Kronzon, I. Intracardiac Echocardiography for Structural Heart and Electrophysiological Interventions. *Curr. Cardiol. Rep.* **2017**, *19*, 102. [[CrossRef](#)]
39. Baran, J.; Stec, S.; Pilichowska-Paszkiel, E.; Zaborska, B.; Sikora-Fraç, M.; Kryński, T.; Michałowska, I.; Łopatka, R.; Kułakowski, P. Intracardiac Echocardiography for Detection of Thrombus in the Left Atrial Appendage. *Circ. Arrhythmia Electrophysiol.* **2013**, *6*, 1074–1081. [[CrossRef](#)] [[PubMed](#)]
40. Saksena, S.; Sra, J.; Jordaens, L.; Kusumoto, F.; Knight, B.; Natale, A.; Kocheril, A.; Nanda, N.C.; Nagarakanti, R.; Simon, A.M.; et al. A prospective comparison of cardiac imaging using intracardiac echocardiography with transesophageal echocardiography in patients with atrial fibrillation: The intracardiac echocardiography guided cardioversion helps interventional procedures study. *Circ. Arrhythmia Electrophysiol.* **2010**, *3*, 571–577. [[CrossRef](#)] [[PubMed](#)]
41. Goldman, M.J. The management of chronic atrial fibrillation. *Prog. Cardiovasc. Dis.* **1960**, *2*, 465–479. [[CrossRef](#)]
42. Manning, W.J.; Leeman, D.E.; Gotch, P.J. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. *J. Am. Coll. Cardiol.* **1989**, *13*, 617–623. [[CrossRef](#)]
43. Scherr, D.; Dalal, D.; Chilukuri, K.; Dong, J.; Spragg, D.; Henrikson, C.A.; Nazarian, S.; Cheng, A.; Berger, R.D.; Abraham, T.P.; et al. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **2009**, *20*, 379–384. [[CrossRef](#)] [[PubMed](#)]
44. Wallace, T.W.; Atwater, B.D.; Daubert, J.P.; Voora, D.; Crowley, A.L.; Bahnson, T.D.; Hranitzky, P.M. Prevalence and clinical characteristics associated with left atrial appendage thrombus in fully anticoagulated patients undergoing catheter-directed ablation of atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **2010**, *21*, 849–852. [[CrossRef](#)] [[PubMed](#)]
45. Anselmino, M.; Garberoglio, L.; Gili, S.; Bertaglia, E.; Stabile, G.; Marazzi, R.; Themistoclakis, S.; Solimene, F.; Frea, S.; Marra, W.G.; et al. Left atrial appendage thrombi relate to easily accessible clinical parameters in patients undergoing atrial fibrillation transcatheter ablation: A multicentre study. *Int. J. Cardiol.* **2017**, *241*, 218–222. [[CrossRef](#)] [[PubMed](#)]
46. Connolly, S.J.; Ezekowitz, M.D.; Yusuf, S.; Eikelboom, J.; Oldgren, J.; Parekh, A.; Pogue, J.; Reilly, P.A.; Themeles, E.; Varrone, J.; et al. RELY Steering Committee and Investigators, Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2009**, *361*, 1139–1151. [[CrossRef](#)] [[PubMed](#)]
47. Patel, M.R.; Mahaffey, K.W.; Garg, J.; Pan, G.; Singer, D.E.; Hacke, W.; Breithardt, G.; Halperin, J.L.; Hankey, G.J.; Piccini, J.P.; et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* **2011**, *365*, 883–891. [[CrossRef](#)] [[PubMed](#)]
48. Granger, C.B.; Alexander, J.H.; McMurray, J.J.; Lopes, R.D.; Hylek, E.M.; Hanna, M.; Al-Khalidi, H.R.; Ansell, J.; Atar, D.; Avezum, A.; et al. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2011**, *365*, 981–992. [[CrossRef](#)]
49. Giugliano, R.P.; Ruff, C.T.; Braunwald, E.; Murphy, S.A.; Wiviott, S.D.; Halperin, J.L.; Waldo, A.L.; Ezekowitz, M.D.; Weitz, J.I.; Špinar, J.; et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2013**, *369*, 2093–2104. [[CrossRef](#)]
50. Russo, V.; Carbone, A.; Rago, A.; Golino, P.; Nigro, G. Direct Oral Anticoagulants in octogenarians with atrial fibrillation: it's never too late. *J. Cardiovasc. Pharmacol.* **2019**, *73*, 207–214. [[CrossRef](#)]

51. Russo, V.; Attena, E.; Mazzone, C.; Melillo, E.; Rago, A.; Galasso, G.; Riegler, L.; Parisi, V.; Rotunno, R.; Nigro, G.; et al. Real-life Performance of Edoxaban in Elderly Patients with Atrial Fibrillation: A Multicenter Propensity Score-Matched Cohort Study. *Clin. Ther.* **2019**. [[CrossRef](#)] [[PubMed](#)]
52. Russo, V.; Rago, A.; Proietti, R.; Attena, E.; Rainone, C.; Crisci, M.; Papa, A.A.; Calabrò, P.; D'Onofrio, A.; Golino, P.; et al. Safety and Efficacy of Triple Antithrombotic Therapy with Dabigatran versus Vitamin K Antagonist in Atrial Fibrillation Patients: A Pilot Study. *BioMed Res. Int.* **2019**, *2019*, 5473240. [[CrossRef](#)] [[PubMed](#)]
53. Russo, V.; Bottino, R.; Rago, A.; Di Micco, P.; D'Onofrio, A.; Liccardo, B.; Golino, P.; Nigro, G. Atrial Fibrillation and Malignancy: The Clinical Performance of Non-Vitamin K Oral Anticoagulants-A Systematic Review. *Semin. Thromb. Hemost.* **2019**, *45*, 205–214. [[PubMed](#)]
54. Russo, V.; Attena, E.; Mazzone, C.; Esposito, F.; Parisi, V.; Bancone, C.; Rago, A.; Nigro, G.; Sangiuolo, R.; D'Onofrio, A. Nonvitamin K Antagonist Oral Anticoagulants Use in Patients with Atrial Fibrillation and Bioprosthetic Heart Valves/Prior Surgical Valve Repair: A Multicenter Clinical Practice Experience. *Semin. Thromb. Hemost.* **2018**, *44*, 364–369. [[PubMed](#)]
55. Russo, V.; Rago, A.; Papa, A.A.; Di Meo, F.; Attena, E.; Golino, P.; D'Onofrio, A.; Nigro, G. Use of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients with Malignancy: Clinical Practice Experience in a Single Institution and Literature Review. *Semin. Thromb. Hemost.* **2018**, *44*, 370–376. [[PubMed](#)]
56. Russo, V.; Rago, A.; Proietti, R.; Di Meo, F.; Antonio Papa, A.; Calabrò, P.; D'Onofrio, A.; Nigro, G.; Alturki, A. Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: The real-life evidence. *Ther. Adv. Drug Saf.* **2017**, *8*, 67–75. [[CrossRef](#)] [[PubMed](#)]
57. Russo, V.; Bianchi, V.; Cavallaro, C.; Vecchione, F.; De Vivo, S.; Santangelo, L.; Sarubbi, B.; Calabro, P.; Nigro, G.; D'Onofrio, A. Efficacy and safety of dabigatran in a “real-life” population at high thromboembolic and hemorrhagic risk: Data from MonaldiCare registry. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 3961–3967.
58. Russo, V.; Rago, A.; D'Onofrio, A.; Nigro, G. The clinical performance of dabigatran in the Italian real-life experience. *J. Cardiovasc. Med.* **2017**, *18*, 922–923. [[CrossRef](#)]
59. Telles-Garcia, N.; Dahal, K.; Kocherla, C.; Lip, G.Y.H.; Reddy, P.; Dominic, P. Non-vitamin K anticoagulants oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: A systematic review and meta-analysis. *Int. J. Cardiol.* **2018**, *268*, 143–148. [[CrossRef](#)]
60. Gibson, C.M.; Basto, A.N.; Howard, M.L. Direct Oral Anticoagulants in Cardioversion: A Review of Current Evidence. *Ann. Pharmacother.* **2018**, *52*, 277–284. [[CrossRef](#)]
61. Itäinen, S.; Lehto, M.; Vasankari, T.; Mustonen, P.; Kotamäki, M.; Numminen, A.; Lahtela, H.; Bah, A.; Hartikainen, J.; Hekkala, A.M.; et al. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients undergoing elective cardioversion. *Europace* **2018**, *20*, 565–568. [[CrossRef](#)] [[PubMed](#)]
62. Frederiksen, A.S.; Albertsen, A.E.; Christesen, A.M.S.; Vinter, N.; Frost, L.; Møller, D.S. Cardioversion of atrial fibrillation in a real-world setting: Non-vitamin K antagonist oral anticoagulants ensure a fast and safe strategy compared to warfarin. *Europace* **2018**, *20*, 1078–1085. [[CrossRef](#)] [[PubMed](#)]
63. Russo, V.; Rago, A.; Papa, A.A.; D'Onofrio, A.; Golino, P.; Nigro, G. Efficacy and safety of dabigatran in patients with atrial fibrillation scheduled for transoesophageal echocardiogram-guided direct electrical current cardioversion: A prospective propensity score-matched cohort study. *J. Thromb. Thrombolysis* **2018**, *45*, 206–212. [[CrossRef](#)]
64. Russo, V.; Di Napoli, L.; Bianchi, V.; Tavoletta, V.; De Vivo, S.; Cavallaro, C.; Vecchione, F.; Rago, A.; Sarubbi, B.; Calabrò, P.; et al. A new integrated strategy for direct current cardioversion in non-valvular atrial fibrillation patients using short term rivaroxaban administration: The MonaldiVert real life experience. *Int. J. Cardiol.* **2016**, *224*, 454–455. [[CrossRef](#)] [[PubMed](#)]
65. Rago, A.; Papa, A.A.; Cassese, A.; Arena, G.; Magliocca, M.C.G.; D'Onofrio, A.; Golino, P.; Nigro, G.; Russo, V. Clinical Performance of Apixaban vs. Vitamin K Antagonists in Patients with Atrial Fibrillation Undergoing Direct Electrical Current Cardioversion: A Prospective Propensity Score-Matched Cohort Study. *Am. J. Cardiovasc. Drugs* **2019**, *19*, 421–427. [[CrossRef](#)]
66. Stabile, G.; Russo, V.; Rapacciuolo, A.; De Divitiis, M.; De Simone, A.; Solimene, F.; D'Onofrio, A.; Iuliano, A.; Maresca, G.; Esposito, F.; et al. Transesophageal echocardiography in patients with persistent atrial fibrillation undergoing electrical cardioversion on new oral anticoagulants: A multi center registry. *Int. J. Cardiol.* **2015**, *184*, 283–284. [[CrossRef](#)] [[PubMed](#)]

67. Papp, J.; Zima, E.; Bover, R.; Karaliute, R.; Rossi, A.; Szymanski, C.; Troccoli, R.; Schneider, J.; Fagerland, M.W.; Camm, A.J.; et al. Changes in oral anticoagulation for elective cardioversion: Results from a European cardioversion registry. *Eur. Heart J. Cardiovasc. Pharmacother.* **2017**, *3*, 147–150. [[CrossRef](#)]
68. Russo, V.; Rago, A.; Papa, A.A.; Bianchi, V.; Tavoletta, V.; DE, S.V.; Cavallaro, C.; Nigro, G.; D'Onofrio, A. Budget impact analysis of rivaroxaban vs. warfarin anticoagulation strategy for direct current cardioversion in non-valvular atrial fibrillation patients: The MonaldiVert Economic Study. *Minerva Cardioangiol.* **2018**, *66*, 1–5.
69. Bertaglia, E.; Anselmino, M.; Zorzi, A.; Russo, V.; Toso, E.; Peruzza, F.; Rapacciuolo, A.; Migliore, F.; Gaita, F.; Cucchini, U.; et al. NOACs and atrial fibrillation: Incidence and predictors of left atrial thrombus in the real world. *Int. J. Cardiol.* **2017**, *249*, 179–183. [[CrossRef](#)]
70. Hwang, J.; Park, H.S.; Jun, S.W.; Choi, S.W.; Lee, C.H.; Kim, I.C.; Cho, Y.K.; Yoon, H.J.; Kim, H.; Nam, C.W.; et al. The incidence of left atrial appendage thrombi on transesophageal echocardiography afterpretreatment with apixaban for cardioversion in the real-world practice. *PLoS ONE* **2018**, *13*, e0208734. [[CrossRef](#)]
71. Klein, A.L.; Grimm, R.A.; Murray, R.D.; Apperson-Hansen, C.; Asinger, R.W.; Black, I.W.; Davidoff, R.; Erbel, R.; Halperin, J.L.; Orsinelli, D.A.; et al. Use of Transesophageal Echocardiography to Guide Cardioversion in Patients with Atrial Fibrillation. *N. Engl. J. Med.* **2001**, *344*, 1411–1420. [[CrossRef](#)] [[PubMed](#)]
72. Corrado, G.; Tadeo, G.; Beretta, S.; Tagliagambe, L.M.; Manzillo, G.F.; Spata, M.; Santarone, M. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* **1999**, *115*, 140–143. [[CrossRef](#)] [[PubMed](#)]
73. Collins, L.J.; Silverman, D.I.; Douglas, P.S.; Manning, W.J. Cardioversion of Nonrheumatic Atrial Fibrillation. Reduced Thromboembolic Complications with 4 Weeks of Precardioversion Anticoagulation Are Related to Atrial Thrombus Resolution. *Circulation* **1995**, *92*, 160–163. [[CrossRef](#)] [[PubMed](#)]
74. Hammerstingl, C.; Pötzsch, B.; Nickenig, G. Resolution of giant left atrial appendage thrombus with rivaroxaban. *Thromb. Haemost.* **2013**, *109*, 583–584.
75. Takasugi, J.; Yamagami, H.; Okata, T.; Toyoda, K.; Nagatsuka, K. Dissolution of the left atrial appendage thrombus with rivaroxaban therapy. *Cerebrovasc. Dis.* **2013**, *36*, 322–323. [[CrossRef](#)]
76. Vidal, A.; Vanerio, G. Dabigatran and left atrial appendage thrombus. *J. Thromb. Thrombolysis* **2012**, *34*, 545–547. [[CrossRef](#)] [[PubMed](#)]
77. Lip, G.Y.; Hammerstingl, C.; Marin, F.; Cappato, R.; Meng, I.L.; Kirsch, B.; van Eickels, M.; Cohen, A. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). *Am. Heart J.* **2016**, *178*, 126–134. [[CrossRef](#)] [[PubMed](#)]
78. Niku, A.D.; Shiota, T.; Siegel, R.J.; Rader, F. Prevalence and Resolution of Left Atrial Thrombus in Patients with Nonvalvular Atrial Fibrillation and Flutter with Oral Anticoagulation. *Am. J. Cardiol.* **2019**, *123*, 63–68. [[CrossRef](#)] [[PubMed](#)]
79. Lee, W.C.; Fang, C.Y.; Chen, Y.L.; Fang, H.Y.; Chen, H.C.; Liu, W.H.; Fu, M.; Chen, M.C. Left Atrial or Left Atrial Appendage Thrombus Resolution After Adjustment of Oral Anticoagulant Treatment. *J. Stroke Cerebrovasc. Dis.* **2019**, *28*, 90–96. [[CrossRef](#)] [[PubMed](#)]

