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REVIEW

Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and atrial thrombosis: An appraisal of current evidence

Les NOAC chez les patients avec fibrillation atriale en cas de thrombose atriale: une révision des preuves actuelles

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Abbreviations: AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (Doubled)—Vascular disease, Age 65—74 years and Sex category (Female); CI, confidence interval; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant; TOE, transoesophageal echocardiogram; VKA, vitamin K antagonist.

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Summary Major thromboembolic complications in patients with atrial fibrillation, secondary to thromboembolism from the left atrium or the left atrial appendage, are a major concern because of their burden of disabling stroke and mortality. To date, non-vitamin K antagonist oral anticoagulants (NOACs) are considered the first-line strategy in most patients with atrial fibrillation receiving chronic anticoagulation, as they have major advantages compared with vitamin K antagonists, including minimization of intracranial bleeding risk. Although several studies and post-hoc analyses have provided initial data on the use of NOACs in patients with documented atrial and/or left atrial appendage thrombosis, the benefit of NOACs in these patients has not been fully elucidated. In this review, we reappraise current evidence supporting the use of NOACs in patients with established atrial and/or left atrial appendage thrombosis, discussing potential mechanisms favouring the use of a NOAC-based strategy in this special setting.

MOTS CLÉS
Fibrillation atriale ;
Oreillette gauche ;
Anticoagulants ;
NOACs ;
Thromboembolie

Résumé Les complications thromboemboliques majeures chez les patients atteints de fibrillation atriale, secondaires à la formation de thrombus dans l'oreillette gauche ou dans l'appendice auriculaire gauche, représentent une préoccupation majeure pour leur charge d'accidents vasculaires invalidants et de mortalité. À ce jour, les anticoagulants oraux non antagonistes de la vitamine K (NOAC) sont considérés comme le premier choix chez la plupart des patients atteints de fibrillation atriale qui nécessitent une anticoagulation chronique car ils présentent des avantages majeurs par rapport aux antagonistes de la vitamine K, tels que la réduction des risques de saignement intracrânien. Bien que plusieurs études et analyses post-hoc aient fourni des données initiales sur l'utilisation des NOAC chez les patients présentant une thrombose auriculaire et/ou appendice gauche documentée, le bénéfice des NOAC chez ces patients n'a pas été entièrement élucidé. Dans cette revue, nous réévaluons les preuves actuelles soutenant l'utilisation des NOAC chez les patients présentant une thrombose atriale et/ou auriculaire gauche établie, en discutant des mécanismes potentiels favorisant l'utilisation d'une stratégie basée sur les NOAC dans ce contexte spécial.

Background

Atrial fibrillation (AF) is by far the most common sustained cardiac arrhythmia worldwide, and is well known to be associated with an average fivefold increase in the risk of thromboembolic events [1,2]. A diagnosis of AF is made in 20—25% of patients experiencing an ischaemic stroke [3], and this percentage rises to 30% among those undergoing prolonged cardiac rhythm monitoring [4]. Published data show that cardioembolic strokes resulting from unrecognized, untreated or undertreated AF account for at least 15% of all cases of ischaemic stroke [1]. To date, non-vitamin K antagonist oral anticoagulants (NOACs) are broadly recommended as first-line therapy in most patients with AF, and are considered an advance compared with the traditional vitamin K antagonist (VKA)-based approach. In large randomized trials, NOACs have shown overall superiority compared with warfarin, mostly minimizing the risk of intracranial bleeding, as well as the most severe bleeding—a well-known determinant of poor outcome. However, the role of NOACs in patients with AF in the presence of documented atrial thrombosis is less well characterized.

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This review aims to reappraise current evidence on the use of NOACs in patients with AF and established atrial and/or left atrial appendage (LAA) thrombosis.

Left atrial anatomical and pathophysiological considerations

Pathological changes in the anatomy/function of the left atrium and LAA are closely related to the development of AF and its complications [5,6]. The relevance of the LAA derives specifically from the remarkable finding that in almost 90% of cases of stroke caused by AF, the LAA is the primary site of thrombus formation [1,7]. The LAA is an embryonic remnant of the primordial left atrium [5,6]; in adults it acts as a haemodynamic reservoir and a determinant of atrial compliance, as well as a source of secretion of atrial natriuretic peptide [5,6]. LAA morphology varies widely in the general population in terms of length (16–51 mm), volume (0.7–19.2 mL) and shape (tubular, elongated, trabeculated or multilobulated) [5,6]. There are four common anatomical variants, classified as ''cactus-like'', ''chicken wing'', ''cauliflower'', and ''windsock'' [8]. Among these, the non-chicken wing variants are associated with a higher risk of silent cerebral embolism and stroke, regardless of the CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age $\geq$ 75 years (Doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (Doubled)–Vascular disease, Age 65–74 years and Sex category (Female)] score [8,9], probably because of the high number of trabeculations and lower flow rates therein [6].

Pathophysiology of left atrial and LAA thrombosis in patients with AF

The mechanisms responsible for thromboembolic events in patients with AF are complex and multifactorial, and can be attributed to three main factors: (1) haemodynamic disturbances (stasis or turbulence); (2) endothelial injury; and (3) activation of blood coagulation (hypercoagulability) [10]. In patients with AF, these three abnormalities coexist, and create a prothrombotic milieu that promotes thrombus formation and embolism (Central illustration), accompanied by the presence of at least moderate mitral stenosis or mechanical valve prosthesis [11].

In patients with AF, atrial paralysis and blood stasis are coupled with slow intra-auricular flows (displayed on echocardiography as spontaneous echo-contrast) [12], low peak velocity ($\leq$ 20 cm/s) of LAA emptying and atrial endocardial abnormalities, which also play a major role [13]. The fibrillating atrium and appendage have a so-called ''rough'' endocardium, typically oedematous, inflamed, fibrotic and dotted with thrombotic formations [6], with a dysfunctional endothelium, as a result of mechanical, oxidative and inflammatory stressors [10], that favour in loco thrombosis. Furthermore, increased exposure of procoagulant/proinflammatory factors on the atrial endocardium (i.e. von Willebrand factor [14–16] and tissue factor [10]) and reduced anticoagulant factors (i.e. thrombomodulin) [17] have been reported, suggesting the co-presence of local and systemic prothrombotic patterns [10,15]. A state of platelet hyper-reactivity and hypofibrinolysis has also been described, with increased levels of tissue plasminogen activator and plasminogen activator inhibitor-1, which are also associated with outcome [10].

NOACs for patients with LAA thrombosis: Current evidence

To date, anticoagulant therapy is the therapeutic gold standard to prevent thromboembolic complications in patients with AF [18,19]. VKAs reduce the risk of stroke/systemic embolism by > 60% and the risk of death by > 25% [3]. The introduction of NOACs has improved management and outcomes in this population, further decreasing stroke/systemic embolism and death by an additional 19% and 10%, respectively [19], and reducing intracranial bleeding by > 50% [20] compared with warfarin.

In the broad population of patients with AF, those with a documented diagnosis of left atrial/LAA thrombosis represent a special subset. VKAs are currently the most widely adopted therapy for the resolution of left atrial/LAA thrombosis, with a success rate of 50–60% at 12 months [21]. However, their efficacy is variable, and is strictly related to duration of treatment and persistence of the international normalized ratio value in the therapeutic range [6]. The uncertainties related to the effectiveness and safety of VKAs make room for the use of NOACs as an interesting alternative in this setting [22], and evidence currently available argues in favour of their possible use in these patients (Table 1). In patients with atrial/LAA thrombosis, the rationale for the use of NOACs is based on their effectiveness in limiting fibrin accretion, thereby favouring endogenous fibrinolysis [23], resulting in the resolution of already formed thrombi. However, it should be pointed out that the available evidence comes mainly from anecdotal studies, clinical cases and studies with small sample sizes.

Dabigatran

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial is the largest study evaluating the incidence of atrial and LAA thrombosis on transoesophageal echocardiography (TOE) in patients on dabigatran versus warfarin, and has reported similar incidence rates in patients treated with the different regimens (1.8% with dabigatran 110 mg, 1.2% with dabigatran 150 mg and 1.1% with warfarin) [24]. Several small studies and case series have reported a lower incidence of atrial thrombosis in patients on dabigatran versus warfarin [25], although the evidence was not univocal. In a Japanese retrospective study (n = 198) [26], atrial thrombosis on precardioversion TOE was found in eight patients on dabigatran (seven on dabigatran 110 mg and one on dabigatran 150 mg), with a second TOE performed in six of these cases, showing early disappearance (within 23 days) in one patient continuing on dabigatran 150 mg, in two patients upon switching from dabigatran 110 mg to dabigatran 150 mg and in two patients upon switching to warfarin. Vidal et al. [27] first reported

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Table 1 Clinical studies and case reports evaluating the efficacy of warfarin and non-vitamin K antagonist oral anticoagulants in the resolution of atrial thrombosis.

Study	Type of study	Patients (*n*)	Clinical condition	Treatment/drug	Follow-up	Endpoints	Outcomes (%)
Bernhardt et al. [21]	Non-randomized, prospective	43	AF and atrial thrombosis	VKAs	12 months	Thrombus resolution	56
Vidal et al. [27]	Case report	1	AF and left auricular thrombosis	D150 BID	13 months	Thrombus resolution	100
Krishnamoorthy et al. [28]	Case report	1	AF and left auricular thrombosis	D150 BID	6 weeks	Thrombus resolution	100
Morita et al. [29]	Case report	1	AF and atrial thrombosis	D150 BID	4 months	Thrombus resolution	100
Shah et al. [30]	Case report	1	AF and atrial thrombosis	D150 BID, switch to warfarin	4 weeks	Thrombus resolution	100
Ferner et al. [32] (RE-LATED AF-AFNET 7)	Randomized, prospective	NA	AF and left auricular thrombosis	D150 BID versus warfarin	6 weeks	Thrombus resolution	Ongoing
Lip et al. [36] (X-TRA)	Non-randomized, prospective	53	AF and left auricular/atrial thrombosis	Rivaroxaban	6 weeks	Thrombus resolution/reduction	60.40
Hammerstingl et al. [33]	Case report	1	AF and left auricular thrombosis	Rivaroxaban	6 weeks	Thrombus resolution	100
Takasugi et al. [34]	Case report	3	AF and left auricular thrombosis	Rivaroxaban	10—32 days	Thrombus resolution	100
Kawakami et al. [38]	Case report	1	AF and left auricular thrombosis	Apixaban	16 days	Thrombus resolution	100

AF: atrial fibrillation; BID: twice daily; D150: dabigatran 150 mg; VKA: vitamin K antagonist.

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a case of left atrial thrombus resolution with dabigatran. Krishnamoorthy et al. [28] and Morita et al. [29] showed the resolution of LAA and left atrial thrombosis after 6 weeks and 4 months of treatment with dabigatran 150 mg, respectively. At variance with such reports, several others have described a therapeutic failure of dabigatran, requiring a switch to warfarin [30] or another NOAC [31]. In the near future, data from the randomized RE-LATED AF-AFNET 7 trial [32] will clarify the efficacy and safety of dabigatran in the resolution of LAA thrombosis, with an endpoint of primary time to thrombus resolution.

Rivaroxaban

Several case reports have suggested rivaroxaban efficacy after 6 weeks of treatment, even in the case of VKA failure [33,34], although cases of therapeutic failure with rivaroxaban have also been described [35]. The multicentre prospective X-TRA study [36] tested the efficacy of rivaroxaban in the treatment of atrial/LAA thrombosis documented on TOE in 53 patients with AF or flutter and an indication to perform cardioversion or arrhythmia ablation. The rate of thrombus resolution at 6 weeks from the start of therapy was 41.5% (95% confidence interval [CI] 28.1—55.9%), with a resolution/reduction of thrombus size in 60.4% of cases (95% CI 46.0—73.6%), in the absence of stroke or thromboembolic events at follow-up. Despite the low-resolution rate observed, probably because of the presence of an old stratified thrombus (76.7% of patients had never received any oral anticoagulant therapy), results from X-TRA indicate that rivaroxaban can be considered a viable option in patients with AF and concomitant atrial/LAA thrombosis. In a recent randomized study by Ke et al. [37], rivaroxaban proved to be more effective than warfarin in the resolution of LA/LAA thrombus in patients with non-valvular AF, especially after 6 weeks of treatment.

Apixaban

To date, few data are available on the efficacy and safety of apixaban in this setting. Some case reports have documented the resolution or size reduction of left atrial/LAA thrombi with apixaban 5 mg twice daily [38] or apixaban 2.5 mg twice daily in elderly patients with renal failure [39]. In the EMANATE study [40], the protocol suggested (but did not mandate) the use of atrial/LAA imaging, leaving the clinical decision to the discretion of the investigator. In the presence of left atrial/LAA thrombosis at imaging, cardioversion was postponed, the anticoagulant was continued according to randomization and imaging was repeated after 3 weeks. Preprocedural imaging was performed in 855 patients (829 undergoing TOE). In 61 of these cases, an atrial/LAA thrombus was identified (30 in the apixaban group and 31 in the heparin/VKA group), and therapy was changed from apixaban to heparin/VKA in only one case. In the apixaban group, 23 out of 30 patients (77%) underwent new TOE, with thrombosis resolution in 12 cases (52%), while in the heparin/VKA group, in 18 out of 31 patients (58%) TOE was repeated, with thrombosis resolution documented in 10 cases (56%) [41].

Edoxaban

Consistent data regarding the efficacy of edoxaban in dissolving documented atrial and LAA thrombosis are currently missing, and edoxaban has been shown to be effective on TOE in only a few cases after 2 weeks of treatment [42]. In this setting, the ongoing open-label EDO-SP-01-2015 (NCT03489395) is investigating the role of edoxaban in patients with non-valvular AF and atrial/LAA thrombosis. A total of 25 patients with newly diagnosed non-valvular AF, left atrial/LAA thrombosis documented by TOE and a CHA_2DS_2-VASC score > 1 will be included in the study (Fig. 1). As the main goal of this study is to evaluate left atrial/LAA thrombus resolution at TOE on edoxaban after 4 weeks, no control group with VKAs is considered necessary, assuming that, for the purpose of this study, the magnitude of the response of warfarin is already satisfactorily known. A secondary aim of this study is to provide data for the planning and design of a larger study, directly comparing edoxaban versus warfarin in the same population.

Left atrial/LAA thrombosis in scheduled cardioversion

In the case of documented left atrial/LAA thrombosis before cardioversion by TOE, whereas VKAs were previously recommended as first-line treatment [43], recent European guidelines [2] have provided a more general recommendation to obtain effective anticoagulation with either VKAs or NOACs. A summary of the evidence regarding anticoagulation therapy in patients scheduled for cardioversion is presented in Table 2 and Fig. 2 [24,41,44—46].

The duration of the arrhythmia is important for thrombus formation in the atria or the LAA. In patients with AF lasting < 48 hours, European [2] and American [47] guidelines recommend considering prompt cardioversion (electrical or pharmacological), without the need for preceding prolonged anticoagulation or TOE [48], which is the gold-standard method for detecting intracardiac thrombi [49] and/or their resolution. Interesting results on thrombus resolution in patients undergoing TOE-guided cardioversion have come from the SAfety of Fondaparinux in transoesophageal echocardiography-guided Electric cardioversion of Atrial Fibrillation (SAFE-AF) study [50]. The authors compared the efficacy and safety of fondaparinux versus standard treatment (unfractionated heparin plus VKA) in patients undergoing scheduled AF cardioversion. After TOE, patients were randomized to fondaparinux or unfractionated heparin plus VKA, and patients with atrial thrombus were treated for 4 weeks before cardioversion. At follow-up, TOE showed a thrombus resolution of 78.6% in the fondaparinux arm versus 50% in the unfractionated heparin plus VKA arm. No differences in terms of effectiveness and safety were found in thrombus-negative patients. This study has shown, for the first time, the effectiveness of fondaparinux in the resolution of atrial thrombi before cardioversion.

Although it is assumed that thrombus formation requires the continuous presence of AF for about 48 hours, studies with TOE have shown the possible formation of thrombus with even shorter time intervals [51]. On the other hand,

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Table 2 Randomized and non-randomized clinical trials evaluating the efficacy and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with persistent atrial fibrillation undergoing electrical cardioversion.

Study	Type of study	Patients (*n*)	Clinical condition	Treatment	Follow-up	Endpoints	Outcomes
Nagarakanti et al. [24]	RE-LY subanalysis	1983	Persistent AF undergoing cardioversion	Warfarin versus D110 BID or D150 BID	3 weeks precardioversion; 30 days postcardioversion	Stroke/systemic embolism	Warfarin 0.60%; D110 0.77%; D150 0.30%
Cappato et al. [44] (X-VeRT)	Randomized, prospective	1504	Persistent AF undergoing cardioversion	Rivaroxaban versus warfarin	3 weeks precardioversion; 42 days postcardioversion	Composite endpoint: stroke/systemic embolism, AMI, cardiovascular death	Rivaroxaban 0.51%; warfarin 1.02%
Flaker et al. [41]	ARISTOTLE subanalysis	540 (743 cardioversion)	Persistent AF undergoing cardioversion	Apixaban versus warfarin	30 days postcardioversion	Stroke/systemic embolism	Apixaban 0%; warfarin 0%
Ezekowitz et al. [40] (EMANATE)	Randomized, prospective	1500	Persistent AF undergoing cardioversion	Apixaban versus warfarin	30 days postcardioversion	Stroke/systemic embolism	Apixaban 0%; warfarin 0.8%
Plitt et al. [46]	ENGAGE-AF subanalysis	365 (632 cardioversion)	Persistent AF undergoing cardioversion	Edoxaban 60/30 mg versus edoxaban 30/15 mg versus warfarin	30 days postcardioversion	Stroke/systemic embolism	Warfarin 0%; edoxaban 60/30 mg 0%; edoxaban 30/15 mg 1.81%
Goette et al. [45] (ENSURE-AF)	Randomized, prospective	2199	Persistent AF undergoing cardioversion	Edoxaban versus enoxa-parin/warfarin	30 days postcardioversion	Composite endpoint: stroke/systemic embolism, AMI, cardiovascular death	Edoxaban 0.5%; enoxa-parin/warfarin 1%

AF: atrial fibrillation; AMI: acute myocardial infarction; cardioversion: electrical cardioversion; D110: dabigatran 110 mg.; D150: dabigatran 150 mg.

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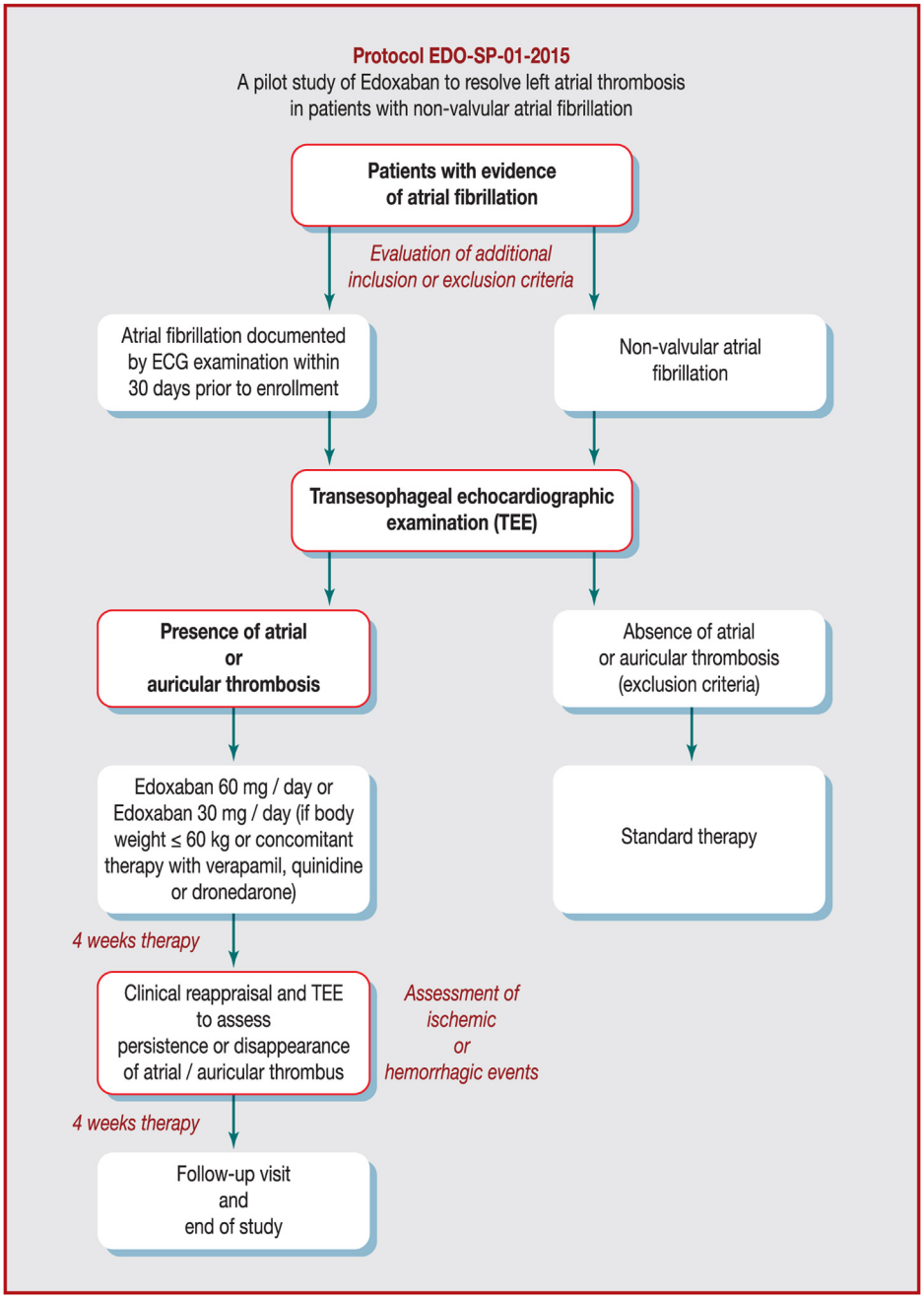

Figure 1. Flow chart of ''A pilot study on Edoxaban for the resolution of left atrial thrombosis in patients with non-valvular atrial fibrillation'' (EDO-SP-01-2015). ECG: electrocardiogram; TOE: transoesophageal echocardiography. [ACVD illustrator: TEE in figure to be changed to TOE].

current evidence and recommendations are moving towards an increasingly early cardioversion strategy after the administration of NOACs [40]. For this reason, one of the unmet needs is to identify the patients most likely to have thrombus, in whom to use a TOE-guided strategy.

Discussion

To date, although none of the NOACs has been tested specifically for the resolution of LA/LAA thrombosis in dedicated large controlled trials, overall evidence generates the hypothesis of their possible effective and safe use in this setting. Whereas most reports suggest that resolving LA/LAA thrombosis is possible with NOACs, and that their effectiveness depends on the duration of treatment, in a percentage of cases no resolution was achieved, with a need to use VKAs.

The pathophysiological mechanisms leading to increased prothrombotic state and LA/LAA thrombosis in patients with AF are complex and multifactorial. Several randomized studies and a meta-analysis of 59 studies [52] described increased levels of coagulation/fibrinolytic system factors, including β-thromboglobulin, D-dimer, thrombin-antithrombin, prothrombin fragment 1+2 and

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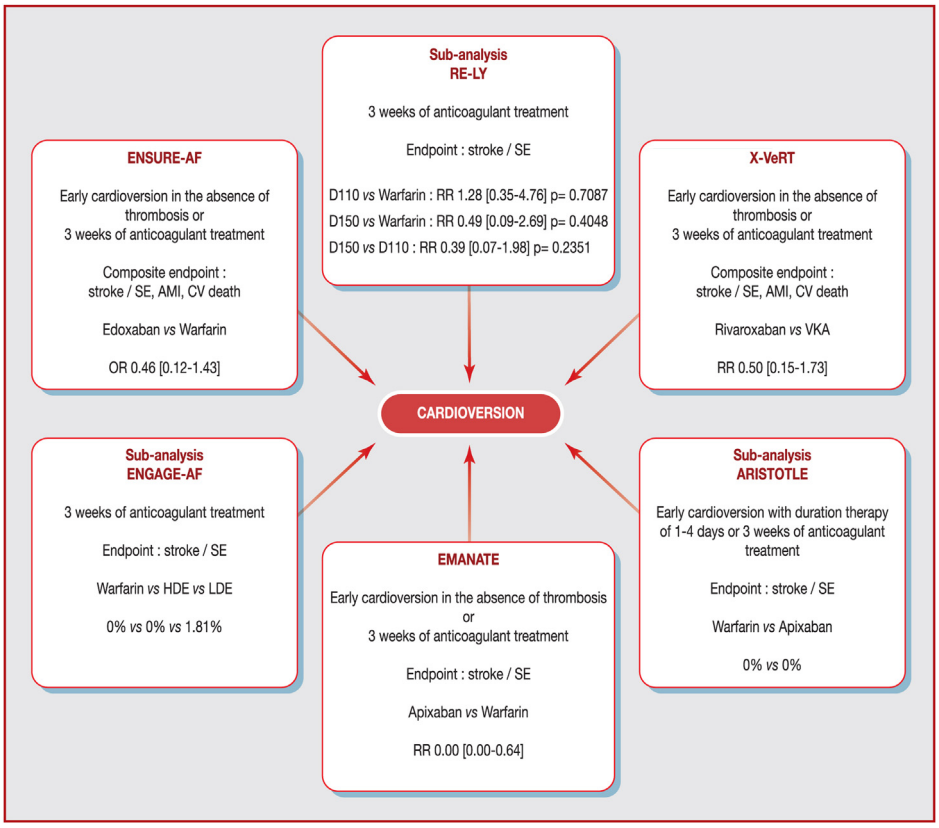

Figure 2. Clinical trial timing of cardioversion and endpoint occurrence in relation to timing of administration of novel oral anticoagulants. AMI: acute myocardial infarction; CV: cardiovascular; D110: dabigatran 110 mg; D150: dabigatran 150 mg; HDE: high-dose edoxaban (60 mg); LDE: low-dose edoxaban (30 mg); OR: odds ratio; RR: relative risk; SE: systemic embolism; VKA: vitamin K antagonists.

antithrombin III, in patients with AF. As only a proportion of patients with AF develop LA/LAA thrombosis, thrombus formation requires additional predisposing factors, including reduced ejection fraction, atrial dilatation and systemic proinflammatory state [53,54].

Considering that NOACs are recommended as first-line therapy in most patients with AF (unless there are contraindications), their initial use might be considered as the default strategy in most cases with documented LA/LAA thrombus. Indeed, although evidence is still sparse, because NOACs are easier to manage in clinical practice and have a better safety profile than VKAs, they represent an attractive alternative in this challenging scenario. From this perspective, a possible decisional algorithm might include the use of VKAs as a second option only, limited to patients reporting NOAC failure. Of note, before choosing VKAs, the switch to a second different NOAC may be a possible alternative, as their therapeutic failure does not represent a class effect. Then, changing NOAC can be sufficient to obtain thrombus resolution in an additional proportion of patients. A major point to be taken into account is that while monitoring adherence to VKAs is possible through dosing international normalized ratio, no tool can effectively demonstrate the adherence (or non-adherence) to NOACs in patients with documented atrial thrombosis. In patients with persistent LA/LAA thrombosis and NOAC failure, therefore, therapeutic adherence evaluation remains mandatory to clarify if NOAC failure was the result of drug inefficacy or was secondary to non-adherence.

Conclusions

To date, AF is a widespread condition with a high economic, social and healthcare impact. Based on a growing body of evidence, NOACs can be considered as first-line therapy in patients with AF and documented left atrial/LAA thrombosis. Additional results from ongoing studies will be useful to confirm current evidence favouring the use of NOACs in these special conditions. Further data are also needed to better define a real-world strategy in these specific case scenarios.

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