REVIEW

Rivaroxaban in atrial fibrillation cardioversion: an update

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Abstract: Currently, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of about 2–3% in the general population, representing a powerful risk factor for stroke and systemic thromboembolism and increased mortality and morbidity. Restoration of sinus rhythm is an important treatment option in AF and has a high success rate, but there is the need for an effective anticoagulation strategy to reduce the risk of embolic events. Anticoagulation with vitamin K antagonists is often associated with failure to achieving effective international normalized ratio. In this setting, recent data have led to extended approval for rivaroxaban in clinical practice, because it is effective and safe in patients with AF undergoing cardioversion, avoiding additional health costs and related time loss, while improving patient satisfaction. The present report provides an overview of the main randomized controlled trial and the main real-life studies, documenting the use of rivaroxaban in patients with non-valvular AF who underwent the cardioversion procedure. Considering that novel non-vitamin K antagonist oral anticoagulants in left atrial appendage thrombi resolution is still unknown in the real-world practice, the main findings on the use of rivaroxaban in this setting are also discussed.

Keywords: atrial fibrillation, cardioversion, novel oral anticoagulants, rivaroxaban, thrombus

Introduction

Atrial fibrillation (AF) is the most frequently occurring arrhythmia and it is estimated that there will be 12.1 million diagnosed cases of AF in 2030 in the US population, with an annual increase in AF prevalence of 4.3%.[1] Currently, AF is considered a powerful risk factor for stroke, independently increasing the risk ≈5-fold across all age groups.[2] In addition, AF is associated with severe complications and increased mortality and morbidity.[3–5] However, the most important clinical trials (PIAF, AFFIRM, RACE, STAF, HOT-CAFE) have not definitively demonstrated the superiority of the rhythm-control vs rate-control strategy.[6–10] These results conflict with data showing that AF is associated with severe complications and increased mortality. This contradiction can be partly explained by the fact that in some of these studies, for example in the AFFIRM study, there was no comparison between sinus rhythm and AF, but between the two different strategies ("rate control vs rhythm-control"); in fact, in the rhythm-control arm only 60% of patients treated with amiodarone were actually in sinus rhythm.[7] A sub-analysis of this trial showed that the presence of sinus rhythm was one of the most powerful independent survival predictors, even after adjusting for other risk factors.[11] Recent guidelines indicate rhythm control strategy precisely for symptomatic patients

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(this is class I indication).[12] However, restoration of sinus rhythm in non-anticoagulated patients is associated with an increased risk of stroke rate by 5–7%.[13–15] It appears clear that in patients scheduled for cardioversion it is necessary to follow a strict anticoagulation protocol that should be started at least 3 weeks before and continued for 4 weeks after if AF is for longer than 48 hrs or has unknown onset ("standard strategy").[12] To allow early cardioversion, transesophageal echocardiography (TEE) can be performed to exclude the majority of left atrial (LA) thrombi ("early strategy").

In patients receiving oral anticoagulant therapy based on vitamin K antagonists (VKAs) (eg, warfarin), therapeutic recommendations include at least 3 weeks of adequate international normalized ratio (INR) control (values between 2.0 and 3.0) before undertaking cardioversion. In the absence of these conditions, the cardioversion procedure must be canceled or postponed. As a consequence, the need for re-planning of the cardioversion procedure can have an organizational impact on hospital facilities.

The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) has simplified the management of anticoagulant therapy, also regarding cardioversion. The advantage of using NOACs compared to warfarin is found in both the "standard" strategy and in the "early" strategy, thanks to the rapid onset of action (average maximum concentration reached after 3 hrs from the time of assumption). In contrast, warfarin therapy must be embraced with low-weight molecular heparin, often without reaching and maintaining the appropriate therapeutic range.[16–18] In fact, nowadays, an increasing number of patients with AF are treated with NOACs instead of, especially due to the lower risk of intracranial bleeding and hemorrhagic stroke as well as a predictable effect without the need for routine INR monitoring.[19,20] In addition, warfarin has also been linked to the progression of arterial stiffness.[21,22] Other advantageous aspects of NOACs are the rapid onset of action (2–4 hrs), shorter half-life and fewer interactions with food and drugs.[23] Furthermore, in vivo studies show that the antioxidant effect of rivaroxaban may protect against systemic oxidant damage induced by peripheral-ischemia reperfusion,[24] which could also be a benefit in patients with AF, considering the involvement of oxidative stress in the pathogenesis of AF.[25]

The first data evaluating the efficacy and safety of NOACs in cardioversion come from post-hoc analyses of the main trials on NOACs in nonvalvular atrial fibrillation (NVAF; ROCKET AF, ARISTOTLE, RELY, ENGAGE AF-TIMI 48)[26–29] and subsequently from trials on NOACs in patients with NVAF undergoing cardioversion (X-VeRT, EMANATE and ENSURE AF).[30–32] Rivaroxaban was the first NOAC studied in patients undergoing cardioversion.

The aim of this review was to highlight findings from recent randomized trials and real-life studies evaluating the use of rivaroxaban in patients with NVAF scheduled for cardioversion to restore sinus rhythm. The resolution of LA appendage thrombus with rivaroxaban is also discussed.

Pharmacokinetics and pharmacodynamics of rivaroxaban

Rivaroxaban is a direct, predictable and dose-dependent inhibitor of factor Xa. The once-daily dose of 20 mg (15 mg in cases of moderate renal insufficiency) has been shown to be effective and safe in randomized clinical trials and real-life studies.[26,33] Furthermore, the once-daily dose has a similar efficacy and safety profile to that of the twice-daily dose of rivaroxaban.[34,35] The once-daily dose of rivaroxaban also permits improved compliance compared to other NOACs.[36] It is rapidly absorbed after oral ingestion and the maximum concentration is achieved after 2–4 hrs from oral intake. To ensure that therapeutic targets are achieved, rivaroxaban should be taken with food to allow an increase in the area under the curve of 80–100%.[37] Approximately, one-third of the drug is directly excreted via the kidneys and the recommended dose of rivaroxaban in subjects with a creatinine clearance of 15–49 mL/min is 15 mg once daily.[38]

Rivaroxaban is contraindicated in Child–Pugh B and C cirrhotic patients but can be prescribed in patients with mild liver failure.[39] The co-administration of rivaroxaban with strong inhibitors of CYP3A4 metabolisers or P-glycoprotein such as antimycotics or HIV protease inhibitors should be avoided.[39,40] In addition, the concomitant use of rivaroxaban with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital or St. John's Wort may lead to reduced rivaroxaban plasma concentrations). Therefore, concomitant administration of strong CYP3A4 inducers should be avoided, unless the patient is closely observed for signs and symptoms of thrombosis.[41,42] Generally, no dose adjustment is required, according to age or gender.[41,42] However, it is recognized that the prevalence of AF increases with age, affecting at least 10% of those ≥75 years.[43] The safe and effective use of rivaroxaban in the elderly is supported by available data from ROCKET AF[20] and XANTUS,[33] but

care must be taken to address comorbidities that may increase the likelihood of bleeding complications, as outlined in recent guidelines.[44,45]

Furthermore, no dose adjustment is required according to ethnicity, only in Japanese patients where 15 mg once daily is the only registered dose.[44] Pharmacokinetic data indicate that rivaroxaban exposure in Japanese patients after 15 mg od is comparable to that in Caucasian patients after 20 mg once daily.[44–46]

Rivaroxaban and sinus rhythm restoration: evidence from clinical trials

A summary of clinical trials on the effect of rivaroxaban and sinus rhythm restoration is shown in Table 1. The ROCKET AF study, published in 2011, was a multicenter, randomized, double-blind, double-dummy, event-driven trial that was conducted at 1,178 participating sites in 45 countries.[20] In this study, it was found that the fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with creatinine clearance of 30–49 mL/min) was superior to dose-adjusted warfarin (INR 2.0–3.0) for the prevention of stroke or systemic embolism among 14,264 patients with NVAF (on-treatment population). Patients enrolled were at a moderate to high risk for stroke (history of stroke, transient ischemic attack (TIA) or systemic embolism or at least two of the following risk factors: heart failure or left ventricular ejection fraction of ≤35%, hypertension, aged ≥75 years or diabetes mellitus). In the primary safety analysis, there was no significant difference between rivaroxaban and warfarin for the risk of major bleeding and in clinically relevant non-major bleeding (14.9% per year in the rivaroxaban group vs 14.5% per year in the warfarin group; HR 1.03; p=0.44), although there was a significant reduction in critical bleeding events: 31% less critical organ bleeding, 33% less intracranial bleeding and 50% less fatal bleeding (on-treatment analysis). However, the reduction in critical bleeding events in the rivaroxaban group was at the cost of increased number of gastrointestinal bleedings; 224 (3.2%) compared with 154 events (2.2%, p<0.001) in the warfarin group.[20]

Results from the ROCKET AF trial remain consistent in the presence of diabetes, renal impairment, heart failure, peripheral artery disease and in elderly patients and in all other sub-groups examined.[47–51] In a post-hoc analysis of the ROCKET AF trial, Piccini et al evaluated outcome, in patients who underwent sinus rhythm restoring procedures: electrical cardioversion (ECV, 143 patients underwent 181 ECV procedures), pharmacological cardioversion (PVC, 142

patients underwent 194 PCV procedures) or AF ablation (79 patients underwent 85 AF ablation procedures).[26] In this subgroup, the rate of stroke or systemic embolism in AF patients with moderate to high risk of stroke was similar between the rivaroxaban and warfarin arms (1.88% in the rivaroxaban arm and 1.86% in the warfarin arm). Furthermore, the incidence of all-cause mortality (1.88% in the rivaroxaban arm vs 3.73% in the warfarin arm), hospitalization (31.3% in the rivaroxaban vs 29.8% in the warfarin arm) and major and non major clinically relevant bleeding (18.8% in rivaroxaban vs 13.0% in warfarin arm) was similar in both groups.[26]

It is important to note that the ROCKET AF study protocol excluded all patients scheduled for ECV or PCV, therefore contributing to the small sample size. Despite this limitation, results derived from the sub-analysis of this study were extremely positive, in terms of efficacy and safety and based on these findings a specific study in this setting was designed; the X-VeRt study.[30] This was the first prospective randomized open-label trial designed to explore the efficacy and safety of the once-daily rivaroxaban dose compared with dose-adjusted VKA treatment (with or without heparin), in anticoagulation-naive or previously treatment-experienced with VKA or NOAC patients undergoing elective cardioversion.

A total of 1,504 patients with hemodynamically stable NVAF of >48 hrs or unknown duration were randomized in a ratio of 2 rivaroxaban: 1 VKA, using two cardioversion strategies. The first approach was early cardioversion (N=872) with the pre-cardioversion anticoagulation therapy of 1–5 days using rivaroxaban or usual therapy (heparin and VKAs). Patients with a LA thrombus detected during the study (using TEE) did not undergo cardioversion. The alternative strategy was a delayed cardioversion of 21–25 days after randomization (N=632). Although the study was not powered for statistical significance, the Steering Committee felt that a descriptive comparison of 1,500 patients would provide clinically meaningful information.[30]

Oral anticoagulation was considered adequate if the INR was maintained in the range 2.0–3.0 and if the pill count of rivaroxaban treatment was ≥80% for 3 consecutive weeks prior to cardioversion. After cardioversion, rivaroxaban or VKAs were continued for 6 weeks and then patients were followed up after 30 days.

The primary efficacy outcome was the composite of stroke or TIA, peripheral embolism, myocardial infarction and cardiovascular death. The cumulative risk for this

Table I Rivaroxaban and sinus rhythm restoration in clinical trials

Author	Study	Intervention	Patients	Primary end point (Rivaroxaban vs Warfarin)	CHA2DS2VASc	Bleeding outcomes (Rivaroxaban vs Warfarin)
Patel et al (2011)[20]	ROCKET-AF (multicenter, randomized, double-blind, double-dummy, event-driven trial)	Rivaroxaban vs warfarin	14.264 non-valvular AF with moderate or high risk of stroke	SSE: PP:1.7% vs 2.2% ($p<0.001$) for non inferiority SP: 1.7% vs 2.2% ($p=0.02$) for superiority ITT: 2.1% vs 2.4% (p-value: 0.01 for non-inferiority; $p=0.12$ for superiority)	Rivaroxaban: 3.48±0.94 (mean) warfarin: 3.46±0.95 (mean)	MNMCRB: 14.9% vs 14.5% ($p=0.44$) IT: 0.5% vs 0.7% ($p=0.02$)
Piccini et al (2013)[26]	ROCKET-AF (retrospective analysis)	Rivaroxaban vs warfarin	375 cardioversion in 285 patients +85 ablation in 79 patients	SSE: 1.88 vs 1.86% ($p>0.05$)	Rivaroxaban: 3 (mean) warfarin: 3(mean)	MNMCRB: 18.75% vs 13.04% ($p=0.46$)
Cappato et al (2014)[30]	X-VeRt (prospective randomized open-label trial)	Rivaroxaban vs VKA therapy	Cardioversion in 1,504 patients	Stroke, TIA, MI, peripheral embolism, CV death: 0.51% vs.1.02% ($p>0.05$)	Rivaroxaban: 0 (or 1, if female only): 147 (14.7) 1 (except for female alone): 215 (21.5) ≥2: 640 (63.9) warfarin: 0 (or 1, if female only): 65 (12.9) 1 (except for female alone) 215: 118 (23.5) ≥2: 319 (63.5)	MB: 0.61% vs 0.80 ($p>0.05$)
Hohnloser et al (2016)[52]	Post-hoc analysis of X-VeRT	Rivaroxaban vs VKAs	705 patients in treatment satisfaction (472 on rivaroxaban and 233 on VKAs) 632 patients in delayed cardioversion strategy	TSQM II questionnaire for Convenience, Effectiveness, and Global satisfaction: 80.32 vs 66.71, 38.76 vs 34.37 and 81.67 vs 67.46 ($p=0.001$ for all interactions) Cardioversion cost saving per patient: € 360 Cardioversion cost saving per 632 patients: € 228 000	NA	NA

Abbreviations: AF, atrial fibrillation; CV death, cardiovascular death; IT, intracranial hemorrhage; ITT, Intention-to-treat population; MB, major bleeding; MI, myocardial infarction; MNMCRB, major and non-major clinically relevant bleeding; NA, not available; PPP, per-protocol, as-treated population; SP, safety, as-treated population; SSE, stroke and systemic embolism; TIA, transient ischemic attack; TSQM II, Treatment Satisfaction Questionnaire for Medication version II; VKA, vitamin K antagonist.

composite outcome was 0.51% for patients in the rivaroxaban group and 1.02% for patients in the VKAs group, with a risk ratio (RR) for rivaroxaban to VKA of 0.50 (95% CI 0.15–1.73). In terms of safety profile, major bleeding occurred in 0.61% patients in the rivaroxaban group and in 0.80% patients in the VKA group (RR: 0.76; 95% CI 0.21–2.67). Although not statistically powered to evaluate the efficacy, as previously described, results of the warfarin arm, however, are perfectly in line with data from other studies and this may be considered an important "surrogate marker" on the reliability of results that were also obtained in the rivaroxaban arm.

These data indicate that rivaroxaban anticoagulation therapy is associated with a reduction in the incidence of thromboembolic events and major bleeding events, that is applicable to both cardioversion strategies. Furthermore, in the early cardioversion group (involving LA thrombi exclusion within TEE), rivaroxaban administration at least 4 hrs before cardioversion was found to be effective and safe. The shorter time to cardioversion in the rivaroxaban arm is one of the most important results that emerged from this study.

Post hoc analyses of Phase III studies with NOACs have shown the efficacy and safety of NOACs in patients with AF undergoing cardioversion.[26–29] Based on these studies, the European Medicines Agency has extended the approved indications for NOACs, therefore to include continued use in cardioversion: "Patients can stay on NOACs while being cardioverted". Furthermore, based on Phase IIIb prospective studies specifically designed for cardioversion, the technical leaflet for some NOACs allows use in naïve patients. Among NOACS, rivaroxaban was the first agent to have the indication extended (19 January 2015; "Xarelto can be initiated or continued in patients who may require cardioversion. For TEE guided cardioversion in patients not previously treated with anticoagulants, Xarelto treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken Xarelto, as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account").[41]

A point of interest is that in the delayed cardioversion group of X-VeRt, cardioversion followed a shorter treatment period with rivaroxaban (mean of 25 days) compared with VKAs (mean of 34 days) because of the inability to achieve adequate anticoagulation prior to cardioversion in the VKA group at 3 weeks (p=0.001). In the delayed group, 321/417

(77%) patients in the rivaroxaban arm compared with 78/215 (36.3%) patients in the VKA arm underwent cardioversion within the target time range (p=0.001), this difference being attributed primarily to failure in achieving anticoagulation target in the VKA group. In summary, the added value from rivaroxaban use emerging from these studies is the possibility of more precise planning of the timing for the cardioversion procedure.

The aforementioned management and practical advantages of rivaroxaban also have important economic repercussions. In fact, in terms of economic impact in the hospital, it has been estimated that the time saved and subsequent lack of rescheduling of cardioversion procedure by using rivaroxaban instead of warfarin (added to cost of drug therapy, INR monitoring and cardioversion procedure) could result in a saving of over €360 per patient and total saving of €228,000, considering 632 patients in Italy. Moreover, Hohnloser et al showed that patients in the rivaroxaban group reported greater satisfaction compared with the VKA group, both in the early and in the delayed strategy, measuring using the vaulted Treatment Satisfaction Questionnaire for Medication version II subscale scores for Convenience, Effectiveness, and Global satisfaction.[52]

Similarly, in patients with AF undergoing elective ECV in the Netherlands it was shown that choosing rivaroxaban instead VKA would have a 49.6% probability of being cost saving (taking into account productivity loss and informal care costs) and would increase a patient's quality of life.[53] The impact of both economic (cost saving), management and patient satisfaction observed in these studies has also been observed in the real-life choice of anticoagulation strategy.

Rivaroxaban and sinus rhythm restoration: evidence from real-life studies

The initial positive results of trials certainly encouraged the use of rivaroxaban in clinical practice. Data emerging from real-life observations have been gaining increasing importance in the eyes of clinicians and decision-makers in public spending. They are considered a complementary confirmation, in terms of efficacy and safety, since they offer additional information to those of randomized controlled trials, thus allowing to describe a picture that is more representative of the reality observed in routine clinical practice. These real-life studies are summarized in Table 2.

Table 2 Rivaroxaban and sinus rhythm restoration in real-life studies

Author	Study design	Population	CHA2DS2VASc	HAS-BLED	Adverse outcome
Camm et al[33]	Outcome within 30 days after cardioversion	502 (391 PC 151 EC)	2.7	1.7	3 (0.6%) TIA 2 (0.4%) MB
Itainen et al[55]	Outcome in patients undergoing cardio-version with NOACs	431 on rivaroxaban	1.8	1.1	1 ischaemic stroke 3 minor bleeding
Fermia et al[56]	Outcome in pts undergoing DCCV on NOACs (8 weeks of follow-up)	60 on rivaroxaban	2		1 major bleeding
Russo et al[57]	Outcome in rivaroxaban short–term administration for TE-guided DCCV in NVAF patients on warfarin with INR not in range	78	4		no

Abbreviations: TEE, transesophageal echocardiography; TIA, transient ischaemic attack; MB, major bleeding; PC, pharmacological cardioversion; EC, electrical cardiover-sion; DCCV, direct current cardioversion; NOAC, non-vitamin K antagonist oral anticoagulent; INR, international normalised ratio.

The panorama of the so-called "real-life" data is quite complex and ranges from Phase IV studies (non-interventional prospective studies), to studies of registries (prospective or retrospective) and analysis of administrative and insurance databases to observations of case reports or case series.

The most robust data from a methodological point of view are certainly those derived from Phase IV studies that have clear endpoints, well-defined definitions of bleeding and above all an independent committee that are blinded to events (eg, randomized controlled trials). The Phase IV study performed with rivaroxaban in the context of NVAF is the XANTUS study.

XANTUS was the first international, prospective, observational study that has assessed the safety and the effectiveness of rivaroxaban in a broad NVAF patient population. A total of 6,784 patients treated with rivar-oxaban across 311 centers in Europe, Israel and Canada 128 patients (2.1 events per 100 patient-year) presented major bleeding, 43 (0.7 events per 100 patient-years) presented a stroke and 118 (1.9 events per 100 patient-year) died, showing that the rates of stroke and major bleeding were very low in patients receiving rivaroxa-ban in routine clinical practice.[33] From the overall popu-lation, 502 underwent cardioversion (391 ECV and 151 PCV); within a period of 30 days after the procedure 3 patients (0.6%) presented a TIA and 2 patients (0.4%) presented major bleeding. Analysis of demographic and clinical characteristics showed as expected, that patients who underwent cardioversion were generally younger than those who did not, and had fewer comorbidities and that is reflected in a lower CHA_2DS_2-VASc score

(2.7 vs 3.4) and lower HAS-BLED scores (1.7 vs 2.0).[54] The studies had very different designs and population but despite these limitations the proportions of patients who experienced a stroke or major bleeding event in X-VeRT were similar to those observed at 42 days after cardioversion in XANTUS (0.2% and 0.6%, respec-tively), underlining that rivaroxaban is associated with a low risk of thromboembolic events and major bleeding in patients undergoing cardioversion (Table 3). The majority of patients who underwent cardioversion did not have any adverse events; the rates of major bleeding and mortality were extremely low in this subgroup, as indeed throughout the XANTUS study. These real-life data confirm the results of the Phase IIIb X-VeRT study, as well as all subsequent post-hoc analyses of the ROCKET AF study, as previously described.

In addition to the XANTUS Phase IV study, there are other real-life publications that include data from registers or databases or simpler case reports. We will now examine the main studies of this type, in the context of cardioversion.

The low incidence of ischemic events and bleeding is also confirmed in the study by Itanien et al which

Table 3 Adverse events in X-VeRT and Xantus trials

n/N (%)	X-VeRT[30]	Xantus[33]
Stroke/non-CNS SE	2/978 (0.20)	1/502 (0.2)
Major bleeding	6/988 (0.61)	3/501 (0.6)
Cardiovascular mortality	4/978 (0.41)	0/502 (0)
All cause mortality	5/978 (0.51)	0/502 (0)

Abbreviations: CNS, central nervous system; SE, systemic embolism.

evaluated 1021 patients undergoing ECV of AF or atrial flutter with NOACs between October 2011 and May 2016.[55] A total of 431 patients were treated with rivaroxaban and of these one patient experienced an ischemic stroke on day 4 after cardioversion and 3 patients experienced a bleeding complication, but not a major bleeding event.

In a retrospective study, Femia et al analyzed patients that underwent ECV from January 2014 to June 2016 comparing anticoagulation with warfarin and the NOACs. From a total of 284 patients, 60 were treated with rivaroxaban. Over a period of 8 weeks, no ischemic stroke occurred and there was only one major bleeding.[56]

The MonaldiVert real-life experience was the first study to investigate the efficacy and safety of short-term rivaroxaban administration for TEE-guided ECV in NVAF patients.[57] Between January 2014 and April 2016 from a cohort of 265 patients with persistent AF, 78 AF patients were enrolled on warfarin for at least 3 weeks who had not achieved adequate pre-procedural anticoagulation, with an INR outside the therapeutic range. All patients received rivaroxaban and were scheduled for TEE-guided ECV. After cardioversion, patients were monitored for 90 days and no cases of stroke, peripheral embolism or major bleeding occurred. It is worth noting that their data show that the 29.4% of AF patients referred to their hospital for ECV and on warfarin therapy for at least 3 weeks were rescheduled to perform the procedure, owing to INR levels outside the therapeutic range.[57] Later, Russo et al performed a budget impact analysis of MonaldiVert.[58] They showed that rivaroxaban was an effective and safe therapeutic strategy, that reduces costs, and saves time in NVAF patients undergoing scheduled ECV. It can therefore be concluded that data from this Italian study are also in line with those from the previously described international study X-VeRT and with all other real-life data showing an excellent efficacy and safety profile of rivaroxaban.

Papp et al created a registry, focusing on NOAC strategies in different European countries.[59] A total of 1,101 patients were registered and most of the cardioversion procedures were electrical (97%). From September 2014 to October 2015, they observed a decline in VKA usage in elective cardioversion, with an increase in rivaroxaban use. This reduction may well be a consequence of the publication of the X-Vert trial in 2014, the first prospective trial that demonstrated the efficacy and safety of a NOAC during cardioversion compared to warfarin.

Resolution of LA thrombus with rivaroxaban

More than 90% of thrombi in patients with NVAF originate in the left atrial appendage (LAA).[60] The incidence of LA/LAA thrombus under treatment with VKAs ranges between 0.6% and 7%[61–63] and LAA thrombi seems to persist in up to 40% of patients under VKA treatment with a poor prognosis.[64] To date, several studies have been performed in order to estimate the incidence of thrombi in AF patients treated with one or other therapeutic strategies.

In a retrospective study, Wyrembak et al estimated that the incidence of LAA thrombus was higher on TEEs performed in patients treated with warfarin (1.55%, 8 of 517) than in those treated with NOAC (0.24%, 1 of 420, p=0.047) within 937 routine pre-AF ablation TEE procedures performed in patients treated for at least 4 consecutive weeks before the TEE with warfarin (N=517) or NOAC (N=420; N=203 rivaroxaban, N=90 apixaban, N=127 dabigatran).[65]

These results were also confirmed by Zylla et al who demonstrated that the prevalence of intracardiac thrombi undergoing therapy with phenprocoumon was significantly higher (17.8%) than in the rivaroxaban group (4.1%) or dabigatran (3.8%) in a high-risk population (median CHA2DS2-VASc score of 4).[66]

Gawałko and coworkers performed a single-center observational study of 1,033 consecutive patients with AF who underwent scheduled TEE before catheter ablation or cardioversion for AF in anticoagulation therapy with VKAs (50.9%); rivaroxaban (26.8%), dabigatran (22.2%) and apixaban (0.1%).[67] A total of 174 patients were excluded because they were without any prior oral anticoagulation or underwent bridging with heparin before TEE or they had discontinued NOACs in the previous 3 weeks. There were no differences in baseline characteristics (including the CHA2DS2-VASc and HAS-BLED scores) as well as in the incidence of LAA thrombus (VKAs, 6.9%; NOACs, 5.5%; p=0.40) and dense spontaneous echo contrast (VKAs, 5.3%; NOACs, 3.3%; p=0.18) between patients on VKAs and those on NOACs. Compared with patients treated with dabigatran, the frequency of LAA thrombus in both NOAC groups was comparable (6.8% in the dabigatran group vs 4.4% in the rivaroxaban group; p=0.29), while dense spontaneous echo contrast occurred more often in dabigatran-treated patients (5.2% vs 1.7%; p=0.06).[67]

The low incidence of thrombi has also been confirmed in a real-life study including AF patients (N=414) who underwent catheter ablation of AF (N=220, 53.1%) or scheduled ECV (N=194, 46.9%) and treated with NOACs.[68] The incidence of LAA/LA thrombi seems to be low (3.6%), regardless of the type of NOAC, depending mostly by CHADS2 and CHA2DS2-VASc scores (in particular, history of heart failure, diabetes and previous stroke/TIA), corroborating findings from other studies.[61,62,65,69]

TEE is considered the gold standard moderately invasive method to examine in detail the LA cavity and LAA with the aim of preventing thromboembolism in patients with AF undergoing ECV. In fact, in cases of LAA thrombus detection, cardioversion must be postponed and TEE assessment is recommended after 3–4 weeks to exclude the presence of thrombus prior to undertaking the cardioversion procedure.[12]

In this regard, the effect of NOACs on intracardiac thrombi has not yet been fully elucidated. A summary of clinical studies evaluating the effect of rivaroxaban on the resolution of LA thrombus is presented in Table 4.

In a study by Wei-Chieh Lee et al undertaken from January 2013 to December 2016, 41 cases of LA or LAA thrombus were detected in NVAF patients by TEE in a retrospective single-center study. Among these, only 22 patients underwent TEE follow-up (19 patients did not undergo follow-up TEE due to patient's refusal, inability to tolerate the procedure or totally dependent status post-cerebral infarction) after anticoagulation therapy with NOACs or warfarin (average follow-up period of 575.2 ±436.7 days). Thrombus resolution was detected in 19 patients enrolled (86.4%).[70] Of these 19 patients, 8 received titration of the dose of NOAC (from inappropriate reduced to recommended dosage and of warfarin out of INR target range and another 5 patients switched from aspirin to NOAC or warfarin). The three patients without LA or LAA thrombi resolution had significantly higher CHADS2/CHA2DS2-VASc score and were all in persistent/long-standing AF, even with a high INR and different NOAC use.

The resolution of thrombi in AF patients has recently been evaluated in a prospective, single-arm, open-label, multicenter (X-TRA study)[71] that explored the first time use of rivaroxaban for the resolution of LA/LAA thrombi in patients (N=60 patients enrolled) with NVAF or atrial flutter who had a TEE-confirmed LA/LAA thrombus. Patients enrolled had to be anticoagulation therapy naïve or untreated within 1 month prior to signing the informed consent form (treatment of up to 72 hrs with VKA,

heparin, or a low molecular weight heparin was allowed before the start of rivaroxaban) or suboptimal or ineffective VKA pretreatment (ie, INR <2.0, documented with at least two consecutive measurements that were at least 24 hrs apart) within the last 6 weeks. Three-quarters of patients had persistent, long-standing persistent, or permanent AF and the median CHADS2 and CHA2DS2-VASc scores were 2 and 4, respectively. The mean NOAC treatment duration was 46 days. The thrombus resolution rate was detected in 41.5% by the patient based on TEE assessments. They were older and had lower CHADS2/CHA2DS2-VASc risk scores. Resolved or reduced thrombus was evident in 60.4% of patients. There were no cases of stroke or non-central nervous system systemic embolism during the treatment period and the follow-up. No patients experienced a major bleeding event. Authors of the X-TRA study concluded that the relatively lower than expected resolution thrombus rate can be explained by the fact that the high percentage of patients who had persistent or permanent AF (76.6%) and had no prior use of an oral anticoagulant (76.7%) and a high possibility that they had "old" LA/LAA thrombi.

Despite the fact that the most frequently used anticoagulant strategy was a VKA (81.4% of patients), the thrombus resolution rate in the CLOT-AF study[71] was 62.5% after an observation period of 3–12 weeks, a resolution rate that was virtually identical to that of X-TRA but observed in a much larger sample size.

The CLOT-AF retrospective registry was performed to understand thrombus-related outcome in AF and atrial flutter patients after standard-of-care anticoagulant treatment (156 patients include from 23 centers of the same 7 countries as in X-TRA). The median CHADS2 and CHA2DS2-VASc scores were 2.0 and 3.0, respectively and 56.4% of patients had persistent, long-standing persistent, or permanent AF. The most frequently used anticoagulant strategy was a VKA (81.4% of patients), nevertheless, the study showed a thrombus resolution rate of 62.5% after an observation period of 3–12 weeks, a resolution rate that was virtually identical to that of X-TRA.[71]

The resolution in thrombus rate was confirmed in a recent single-center retrospective study in which no significant difference was observed between warfarin or NOACs (55% vs 66%, respectively)[72] including some case reports[73–77] (see Table 4).

The efficacy of rivaroxaban to dissolve LAA thrombus has also been described in patients who are non-responsive to warfarin because of thrombophilic conditions.[78,79]

Table 4 Rivaroxaban and resolution of left atrial thrombus with rivaroxaban

Author	Intervention	Patients	Results
Lee et al (2018)[71]	Warfarin or NAOC (retrospective single-center study)	22 AF patients in TEE follow-up for LA or LAA thrombus	TEE thrombus resolution in 19 patients enrolled (86.4%) with average follow-up period of 575.2±436.7 days.
Lip et al (2016)[72]	Rivaroxaban 6 weeks therapy (prospective, single-arm, open-label, multicenter study)	60 patients with LA/LAA thrombus	-Thrombus resolution rate was 41.5% -Resolved or reduced thrombus rate was 60.4% -No stroke or major bleeding events
Niku et al (2018)[73]	NAOC (54% on rivaroxaban) or warfarin (retrospective single-centre study)	117 patients with LA/LAA thrombus	Thrombus resolution rate was 59% at follow-up TEE performed within 1 year
Hammerstingl et al (2013)[74]	Phenprocoumon switched to rivaroxaban	1 AF patient case of not resolution of atrial appendage thrombus after 6 weeks of VKA therapy with levels of INR ranging between 2.5 and 3.5	-TEE thrombus size decreased after 4 weeks of rivaroxaban treatment -TEE complete thrombus resolution after 6 weeks of rivaroxaban treatment
Takasugi et al (2013)[76]	Rivaroxaban (10 mg/day) after intravenous UFH infusion	3 AF patients cases of brain MRI of acute infarction and TEE LA thrombus	TEE thrombus resolution after 1–5 weeks of rivaroxaban treatment
Saito et al (2014)[78]	Rivaroxaban (15 mg/day)	1 AF patient case of acute cardioembolic stroke and TEE LA thrombus	TEE thrombus resolution and the smoke-like echo reduction at day 40

Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; LA, left atrium; LAA, left atrial appendage; UFH, unfractionated heparin; NAOC, non-vitamin K antagonist oral anticoagulants; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; VKA, vitamin K antagonist.

The rivaroxaban efficacy in promoting the dissolution of LAA thrombus could be explained by direct inhibition of free and thrombus-associated FXa and prothrombinase activity with consequent reduction of thrombin generation, causing a looser clot that is more sensitive to fibrinolytic enzymes.[80] Furthermore, the inhibitory effect of rivaroxaban on thrombin generation could shift the physiological balance between coagulation and fibrinolysis toward the latter, favoring the resolution of the thrombus.

D-dimer is a known marker of thrombogenesis and high D-dimer levels seem to be an independent predictor of the presence of LAA thrombus.[81] Furthermore, D-dimer levels are reduced by anticoagulation and sinus rhythm restoration in AF patients.[82]

Previous studies have shown that factor Xa exhibits pro-inflammatory activity,[83] therefore inhibiting Xa using rivaroxaban may involve another mechanism of action that is useful for the resolution of thrombi in AF patients. The relationship between plasma biomarkers (indicative of thrombogenesis, fibrinolysis and inflammation: D-dimer, plasminogen activator inhibitor-1 (PAI-1), prothrombin fragment 1+2 (F1,2), thrombin–antithrombin (TAT) complexes, von Willebrand factor (vWF), high-sensitivity interleukin-6 (hsIL-6) and high-sensitivity C-reactive protein (hsCRP)) and LA thrombus resolution after rivaroxaban treatment in the X-TRA study population is recently analyzed by Miyazawa et al.[84] They did not observe any significant associations between thrombus outcomes and thrombogenesis/fibrinolysis biomarker levels or changes in thrombogenesis/fibrinolysis biomarker levels from baseline to end of treatment (mean levels of hsCRP, D-dimer, vWF and TAT decreased from baseline to end of treatment with rivaroxaban). High levels of inflammatory biomarkers in AF patients with LA/LAA thrombus were associated with thrombus resolution or reduction with rivaroxaban treatment.

Rivaroxaban reversal

Rivaroxaban, like other NOACs have short half-lives, with anticoagulant effects significantly reduced within 24 hrs of the last dose.[23] Furthermore, some situations associated with a high risk of bleeding can require emergency reversal, necessitating urgent intervention (spontaneous bleeding from overdose or in the cases of traumatic injury requiring urgent surgical intervention).[85,86]

In May 2018, following results from the ANNEXA-4 trial, the US Food and Drug Administration approved andexanet alfa as the first specific antidote for the anti-Xa inhibitors apixaban and rivaroxaban when reversal of anticoagulant effects is required in life-threatening or uncontrolled bleeding.[87,88] In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hrs.[88] Intravenous andexanet alfa is currently under regulatory review in the EU.[87]

Oral activated charcoal may also be considered for reducing the absorption of apixaban or rivaroxaban.[89]

Limitations

The present review was specifically aimed to highlight findings from recent randomized trials and real-life studies evaluating the use of rivaroxaban in patients with NVAF scheduled for cardioversion to restore sinus rhythm. Several other pleiotropic effects of rivaroxaban are increasingly recognized that have not been addressed in this review. Besides antioxidant effects observed in-vivo that may protect against systemic oxidant damage by peripheral-ischemia reperfusion,[24] rivaroxaban has also been shown to improve survival rate in a murine model of ischemia-reperfusion injury in mice.[91] This may be attributed to improvement in cardiac function through a reduction in inflammatory and fibrotic factors. In another in-vivo model of intermittent hypoxia and cardiac remodeling, rivaroxaban was shown to attenuate both atrial and ventricular remodeling induced by intermittent hypoxia through the prevention of oxidative stress and fibrosis by suppressing the activation of extracellular signal-regulated kinase and nuclear factor-κB pathways via protease-activated receptor-2.[92] Since patients with obstructive sleep apnea (OSA) have a high prevalence of AF, treatment with rivaroxaban could potentially become a novel therapeutic strategy for cardiac remodeling in patients with OSA and AF. These observed pleiotropic cardio-protective effects are mainly limited to in-vivo studies and although some clinical evidence is emerging documenting the anti-oxidant and anti-inflammatory effects,[93] additional clinical studies are needed to verify whether these protective effects can be observed in this setting. Another limitation of the present review was that we focused on rivaroxaban, which is only one of four commercially available NOACs, which all have proven efficacy and safety. We chose to focus on rivaroxaban because we have extensive long-term use of this NOAC and that it can be administered as monotherapy.

Another weakness was that this review did not consider all available literature, since it was not our objective to undertake a systematic review. This review has focused on registered trials and real-life studies.

Conclusion

The strong scientific evidence available demonstrates that NOACs are preferable to VKA in patients with NAVF (this position is supported by the most recent European and American guidelines) and in particular in CHA2DS2-VASc risk scores ≥1 patients scheduled for cardioversion it is reasonable to prefer rivaroxaban instead of VKA anticoagulation therapy.[38,90] The advantage of being able to use rivaroxaban is particularly evident in programmed cardioversion procedures, as previously discussed, but also for patients who have relapses of AF and access the Emergency Department or a specialist clinic. In fact, patients receiving oral anticoagulant therapy based on VKAs (eg, warfarin), therapeutic recommendations include at least 3 weeks of adequate INR control (values between 2.0 and 3.0) before undertaking cardioversion. In the absence of these conditions, the cardioversion procedure must be canceled or postponed. The need for re-planning of the cardioversion procedure has an organizational impact on the hospital facilities, due to either the lack of use of health care services and/or need to occupy health services for a subsequent deadline. The main advantage of rivaroxaban use is the shorter time to cardioversion, compared to VKA therapy, because of the inability to achieve adequate anticoagulation prior to cardioversion using VKA therapy. Actually, rivaroxaban has a rapid onset of action (2–4 hrs) and a more predictable pharmacokinetic and pharmacodynamic profile and has fewer drug–drug interactions than VKAs. In addition, INR measurement is not required. Significant reduction in time is associated with reduced in health care costs. Moreover, these benefits translate into greater satisfaction for NVAF patients and improved quality of life.

In conclusion, rivaroxaban seems to have the same effectiveness as VKA on the resolution of the thrombus and in some cases even superiority.

Future perspectives

Despite the overall evidence for the use of NOACs, there are specific situations for which there is still a lack of clinical evidence. There is still little evidence in the context of thrombus in the atrium, although NOACs have shown positive results in terms of efficacy. Further studies in this setting evaluating rivaroxaban vs standard therapy (VKA) or even

comparison to VKA at a higher INR (between 2.5 and 3.5; as is often the case in clinical practice, although not recommended in guidelines) are warranted. In addition, studies designed ad hoc for special populations, which we increasingly encountered in clinical practice, such as patients on dialysis, patients with extreme weights (underweight and obese) and elderly patients, will aid our understanding of the use of this treatment in these patients.

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Disclosure

The authors report no conflicts of interest in this work.

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