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Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: the real-life evidence

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***Abstract*:** The aim of our article is to provide a concise review for clinicians entailing the main studies that evaluated the efficacy and safety of target-specific oral anticoagulants (TSOAs) for thromboembolic stroke prevention in the real-world setting. Atrial fibrillation (AF) is one of the most common supraventricular arrhythmias that requires anticoagulation therapy to prevent stroke and systemic embolism. TSOAs, dabigatran, apixaban and rivaroxaban have become available as an alternative to warfarin anticoagulation in nonvalvular atrial fibrillation (NVAF). Randomized clinical trials showed non-inferior or superior results in efficacy and safety of the TSOAs compared with warfarin for stroke prevention in NVAF patients. For this reason, the 2012 update to the European Society of Cardiology guidelines for the management of AF recommends TSOAs as broadly preferable to vitamin K antagonists (VKAs) in the vast majority of patients with NVAF [Camm *et al.* 2012]. Although the clinical trial results and the guideline's indications, there is a need for safety and efficacy data from unselected patients in everyday clinical practice. Recently, a large number of studies testing the efficacy and the safety of TSOAs in clinical practice have been published. The aim of our article is to provide a concise review for clinicians, outlining the main studies that evaluated the efficacy and safety of TSOAs for thromboembolic stroke prevention in the real-world setting.

Keywords: apixaban, atrial fibrillation, dabigatran, efficacy, novel oral anticoagulant, real life, rivaroxaban, safety, stroke

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Introduction

Nonvalvular atrial fibrillation (NVAF) is one of most common supraventricular arrhythmias. Anticoagulant therapy is necessary in the majority of patients to prevent the risk of ischemic stroke. CHA_2DS_2Vasc Score is a validated score of stroke risk estimation to decide which patients with NVAF are likely to benefit from anticoagulant therapy. According to the European Society of Cardiology, a score $\geqslant 1$ advises anticoagulation, also evaluating individual hemorrhagic risk with the HAS-BLED score [Lip *et al.* 2011]. Until 2011, warfarin, a vitamin K antagonist (VKA), was the only anticoagulant therapy available for the anticoagulation treatment of atrial fibrillation (AF), considering there is now alternative therapy, such as percutaneous left atrial appendage closure for patients with contraindication to oral anticoagulant therapy (TAO) or those that experienced an ischemic event with TAO [Proietti *et al.* 2015a]. However, the difficulties in achieving optimal anticoagulation with warfarin therapy, related to its slow onset of action, variable pharmacologic effects, numerous food and drug interactions and periodic closely target international normalized ratio (INR) monitoring [Landefeld and Beyth, 1993; Proietti *et al.* 2015b] make difficult the therapeutic management in clinical practice and reduce the real-life patients' compliance. All these challenges have prompted the extensive research and development of target-specific oral anticoagulants (TSOAs) that are now available for stroke prevention in NVAF and are used in various clinical settings [Stabile *et al.* 2015, Russo *et al.* 2016].

Dabigatran

Dabigatran etixilate (DAB) is an oral anticoagulant prodrug that has emerged as the first of a new generation of anticoagulants with the potential to replace warfarin in the appropriate clinical situation. The mechanism of action is competitive direct inhibition of free and clot-bound thrombin. Its pharmacokinetic profile provides fixed twice-daily oral administration and doesn't require routine INR monitoring. Elimination is predominantly *via* renal clearance, with no significant hepatic contribution, and differences in pharmacokinetics are attributed primarily to variations in renal function.

The RE-LY study [Connolly *et al.* 2009a] was a prospective, randomized and open, with blinded adjudication of events, clinical trial of 18,113 patients with AF who were randomized to warfarin or one of two doses of DAB (110 mg bid or 150 mg bid). The trial population consisted of patients with typical AF and cardiovascular/thromboembolic risk: average age 72 years, mean CHADS score 2.1, and history of myocardial infarction (17%), stroke (20%), and heart failure (32%). Half the patients had no previous exposure to warfarin treatment. No data about hemorrhagic risk were given in the RE-LY trial, although according to Eikelboom and colleagues' analysis, 10.4% of the RE-LY study population taking dabigatran 150 and 110 mg bid had a HAS-BLED score $\geqslant 3$ [Eikelboom *et al.* 2013].

RE-LY results showed that both DAB doses (150 mg bid and 110 mg bid) were non-inferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism: 182 patients receiving 110 mg of DAB bid (1.53% per year), 134 patients receiving 150 mg of DAB bid (1.11% per year), and 199 patients receiving warfarin (1.69% per year). The 150 mg bid dosage of DAB was also superior to warfarin (relative risk, 0.66; 95% confidence interval (CI), 0.53–0.82; $p < 0.001$) in preventing stroke or systemic embolism; and the 110 mg bid dosage was superior to warfarin with respect to major bleeding; while the rate of intracranial hemorrhage with both dosages of DAB was less than one third the rate with warfarin without a reduction in the efficacy against ischemic stroke.

Effectiveness and safety of dabigatran in 'real life'

To date, two large database studies in Denmark [Larsen *et al.* 2013] and the USA [Graham *et al.* 2015] examined the real-world experience of DAB compared with warfarin.

From the Danish Registry of Medicinal Product Statistics [Larsen *et al.* 2013] Larsen and colleagues identified a DAB-treated group and a 1:2 propensity-matched warfarin-treated group of 4978 and 8936, respectively, with a mean age of 70.8 years and a mean $CHADS_2$ score of 1.6 [Larsen *et al.* 2013]. According to the main findings, broadly consistent in a subgroup analysis of DAB users with $\geqslant$1-year follow up, the incidence of stroke and systemic embolism was not significantly different between the warfarin- and DAB-treated patients. Adjusted mortality was significantly lower with both DAB doses [110 mg bid: propensity-matched group-stratified hazard ratio (aHR), 0.79; 95% CI, 0.65–0.95; 150 mg bid: aHR, 0.57, 95% CI, 0.40–0.80] when compared with warfarin. Less intracranial bleeding was seen with both DAB doses (110 mg bid: aHR, 0.24; 95% CI, 0.08–0.56; 150 mg bid: aHR, 0.08; 95% CI, 0.01–0.40). The incidence of myocardial infarction (MI) was lower with both DAB doses (110 mg bid: aHR, 0.30; 95% CI, 0.18–0.49; 150 mg bid: aHR, 0.40; 95% CI, 0.21–0.70). Gastrointestinal bleeding was lower with DAB 110 mg bid. (aHR, 0.60; 95% CI, 0.37–0.93) compared with warfarin, but not DAB 150 mg bid.

Larsen and colleagues concluded that efficacy in terms of stroke and systemic embolism prevention was similar between warfarin and DAB (both doses), whereas mortality, PE, and MI were lower with both doses of DAB, in this 'everyday clinical practice' post-approval clinical cohort [Larsen *et al.* 2013]. With regard to safety, major bleeding was similar between DAB and warfarin, whereas intracranial bleeding was lower with both DAB doses, compared with warfarin. Also, the rate of gastrointestinal bleeding was significantly lower in the dabigatran 110-mg b.i.d. treated groups compared with warfarin.

The US Food and Drug Administration (FDA) Medicare analysis [Graham *et al.* 2015] included 67,494 patients who started DAB (150 mg bid and 75 mg bid) and 273,920 patients who started warfarin for NVAF between October 2010 and December 2012 and were older than 65 years. According to the main results, DAB 150 mg bid was associated with reduced risk of ischemic stroke (aHR 0.70; 95% CI, 0.57–0.85; −20%), intracranial hemorrhage (aHR 0.30; 95% CI, 0.21–0.42; −66%) and mortality for all causes (aHR 0.76; 95% CI, 0.67–0.86; −14%) with an increased risk of major gastrointestinal bleeding (aHR 1.51; 95% CI, 1.32–1.73). Subgroups

analysis showed a significant reduction in mortality for all patients over 65-years old except for women over 85-years old. The absolute incidence of ischemic stroke, major gastrointestinal bleeding, intracranial hemorrhage and death was substantially higher during the first 90 days of therapy than during later time periods for both DAB and warfarin. In the DAB-treated group, approximately 16% of patients (10,522 patients) received DAB 75 mg bid and among these, none of the outcome comparisons were statistically significantly different from warfarin except for a lower risk of intracranial hemorrhage with DAB (aHR 0.46; 95% CI, 0.26–0.81). Graham and colleagues concluded that, in general practice settings, DAB was associated with reduced risk of ischemic stroke, intracranial hemorrhage and death, and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with NVAF [Graham *et al.* 2015]. These associations were most pronounced in patients treated with DAB 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with DAB.

The MonaldiCare study is the largest Italian observational registry [Russo *et al.* 2015], which has evaluated the real-life efficacy and safety of both doses of DAB (150 mg bid and 110 mg bid) in a large cohort of patients with NVAF having high thromboembolic (CHA_2DS_2Vasc Score $\geqslant$ 3) and hemorrhagic risk (HAS-BLED $\geqslant$ 3). The MonaldiCare study included 2108 patients (mean age 69.4 $\pm$ 9.4 years) who started the TAO with DAB 110 mg twice daily (DAB 110; n = 1075; 51%) or 150 mg twice daily (DAB 150; n = 1033; 49%), prospectively enrolled between June 2013 and December 2014, and followed for a mean follow up of 18 $\pm$ 9 months. In the MonaldiCare population we reported an ischemic stroke rate of 0.05% and a bleeding complication rate of 0.1%, much lower than the 2.87 % and 3.32% major bleeding rate described in the RE-LY group taking respectively, DAB 110 and 150 mg, and also than the 4.3% annual rate described in the Medicare population. We hypothesized that the low rate of reported adverse events might be related to the patient-centered tailoring approach used for choosing the optimal dosage of DAB. The evidence of the clinical trials and registries were corroborated by a recent observational study that evaluated 442 patients with DAB and 478 patients with acenocoumarol, followed for 1.5 $\pm$ 0.56 years [Korenstra *et al.* 2016]. The results showed an incidence rate of stroke or systemic embolism of 0.8% per year in DAB-treated patients *versus* 1.0% per year in acenocoumarol-treated patients; and an incidence rate of major bleeding of 2.1% per year in DAB-treated patients *versus* 4.3% per year in acenocoumarol-treated patients. Korenstra and colleagues concluded that in 'real-world patients' with AF, DAB appears to be as effective, but significantly safer than acenocoumarol [Korenstra *et al.* 2016].

The recent approval of idarucizumab, a monoclonal antibody fragment, completely reversed the anticoagulant effect of DAB within minutes and should make even safer the DAB administration [Pollack *et al.* 2015]. Additional real-world data will help to increase our understanding of the role of idarucizumab in situations and patient groups in which it can improve clinical outcomes.

Persistence and adherence to dabigatran

In a retrospective study of 86,210 NVAF patients initiating treatment with DAB (46.7%) *versus* warfarin (53.3%), using longitudinal electronic medical records and administrative claims from the US Department of Defense, a consistently higher persistence with therapy in those treated with DAB than in those treated with warfarin at both 6 months (72% *versus* 53%) and 1 year (63% *versus* 39%) was found [Zalesak *et al.* 2013]. Persistence was defined in terms of a permissible medication gap and was higher for DAB using both a 30- and a 60-day permissible gap. Zalesak and colleagues concluded that patients who initiated DAB treatment were more persistent than patients who began warfarin treatment [Zalesak *et al.* 2013]. Within each cohort, patients with lower stroke risk were more likely to discontinue therapy. In a national cohort study of 5376 patients with NVAF initiated on DAB between October–2010 and September–2012 at all Veterans Affairs hospitals, the adherence to the therapy during the first year, calculated as proportion of days covered (PDC) and association between PDC and outcomes, was 72% [Shore *et al.* 2015].

Apixaban

Apixaban is an oral direct factor Xa inhibitor which leads to decreased thrombin generation

and blood clot formation [Heidbuchel *et al.* 2015]. It has a rapid onset of action with peak plasma levels occurring 1–4 hours after oral intake. Apixaban has an elimination half-life of 12 hours and is dosed twice daily [Heidbuchel *et al.* 2015; Bhanwra and Ahluwalia, 2014]. There is no available measure of drug activity outside of certain research labs. In addition, there are fewer interactions with other drugs compared with warfarin [Gassanov *et al.* 2012]. Apixaban was shown to be superior to warfarin in preventing stroke or systemic embolism in NVAF in the ARISTOTLE trial [Granger *et al.* 2011]. In addition, it was demonstrated to be non-inferior to warfarin for the treatment of venous thromboembolism in the AMPLIFY trial [Agnelli *et al.* 2013]. In both trials, apixaban demonstrated a significantly lower risk of both major and minor bleeding compared with warfarin [Granger *et al.* 2011; Agnelli *et al* 2013]. In the AVERROES trial, patients who were considered unsuitable to receive warfarin due to their bleeding risk were randomized to apixaban *versus* aspirin; apixaban significantly reduced the risk of stroke or systemic embolism without significantly increasing the major bleeding risk [Connolly *et al.* 2011].

Effectiveness of apixaban

Data regarding the effectiveness of apixaban outside the controlled environment of randomized clinical trials are scant compared with rivaroxaban and DAB, but the available data are encouraging, with more expected in the near future. Banerjee and colleagues used data from the Danish National Patient Registry to predict the net clinical benefit of new oral anticoagulants, compared with warfarin. Across all subgroups of CHADS2-VASc and HASBLED scores, apixaban had a net clinical benefit compared with warfarin; the net clinical benefit included strokes and major bleeding. In the same study, apixaban was comparable with DAB and rivaroxaban in net clinical benefit [Banerjee *et al.* 2012]. Pisters and colleagues performed a modeling exercise using a large European prospective cohort with a total of 2485 patients included in the analysis. During the 1-year follow up, 3.3% of patients experienced thromboembolism with 1.9% and 5% having a major bleed and dying, respectively. The use of apixaban instead of warfarin, based on the model, would have decreased thromboembolism by 25%, major bleed by 75% and death by 12% [Pisters *et al.* 2013].

Given the establishment of warfarin as the standard of care for anticoagulation to prevent thromboembolism in AF, there is no equipoise for comparisons with placebo and indeed, the efficacy and safety had been clearly established over warfarin and aspirin in the ARISTOTLE and AVERROES trials, respectively [Granger *et al.* 2011; Connolly *et al.* 2011]. McMurray carried out a putative analysis using trial data for apixaban and using the placebo data from warfarin and aspirin comparisons with placebo. The imputed analysis suggests that apixaban reduces all-cause mortality by 33% compared with placebo [McMurray, 2012].

Safety of apixaban

Safety is an integral part of any drug used in medicine; this is truer with anticoagulants given that their use is marred by bleeding [Chen *et al.* 2015]. The significance of bleeding with anticoagulation is illustrated by the use of a risk-benefit ratio to ascertain whether the risk of bleeding is offset by thromboembolisms prevented [January *et al.* 2014]. Apixaban had the strongest association with decreased risk of bleeding compared with warfarin in the randomized trials [Granger *et al.* 2011; Connolly *et al.* 2009b; Ruff *et al.* 2014].

Kamble and colleagues performed a retrospective cohort study of 26,604 patients followed from January 2012 through to December 2013 who were receiving warfarin, apixaban, DAB and rivaroxaban [Kamble *et al.* 2015]. The unadjusted incidence rates of major bleeding per 100 person years were 2.17, 2.98, 3.99 and 4.66 for apixaban, DAB, rivaroxaban and warfarin, respectively. This yielded adjusted hazard ratios (HRs), referenced to warfarin, of 0.53 (0.29–0.97), 0.82 (0.58−1.16) and 1.08 (0.85−1.39) for apixaban, DAB and rivaroxaban, respectively [Kamble *et al.* 2015]. These results were corroborated by two similar studies [Amin *et al.* 2014; Tepper, 2015].

In another study, Lip compared major bleeding risk among newly anticoagulated NV AF patients who were started on warfarin, DAB, rivaroxaban and apixaban; the analysis included 29,338 and the mean follow up was 120 days. Compared with apixaban, the other three drugs had a higher incidence of major bleeding: DAB HR, 1.71; 95% CI, 0.94–3.10, warfarin HR, 1.93; 95% CI, 1.12–3.33 and rivaroxaban HR, 2.19; 95% CI, 1.26–3.76 [Lip, 2015].

Discontinuation and reversibility

A major issue with most medication, and especially anticoagulation, is discontinuation. Pan and colleagues reported on a retrospective cohort study of 24,596 patients who were taking oral anticoagulants. They found a much lower discontinuation rate with apixaban as compared with warfarin (HR 0.55; CI, 0.46–0.66). In addition, apixaban had a lower discontinuation rate compared with DAB (HR 0.55; CI, 0.46–0.66) and rivaroxaban (HR 0.68; CI, 0.57–0.82); these results were over a follow-up period of 210 days [Pan *et al.* 2014]. The reluctance to prescribe Direct oral anticoagulants (DOACs) stems in part from inability to reverse its anticoagulant effect. A benefit of apixaban is the availability of a smaller dose for patients who are older, have low weight and with impaired renal function; essentially, patients who are at an increased risk for bleed [Heidbuchel *et al.* 2015]. Given this benefit over other DOACs, the development of a reversal agent, andexan*et al*pha, will likely lead to an increase in the use of apixaban; andexanet reverses factor Xa inhibition and is therefore also effective for rivaroxaban [Ghadimi *et al.* 2016]. Siegal and colleagues recently demonstrated in the ANNEXA-A study the reversibility of the effect of apixaban in healthy volunteers [Siegal *et al.* 2015]. The study randomized 65 patients to andexanet *al*pha *versus* placebo in a 3:1 ratio. The use of the andexanet bolus resulted in a mean [± SD] reduction, 94 ± 2% *versus* 21 ± 9%; $p < 0.001$ in factor Xa activity that persisted for 2 hours in keeping with the half-life of the drug. If an infusion was used, the effect persisted longer [Siegal *et al.* 2015]. These results show much promise for the reversibility of the effect of apixaban.

Rivaroxaban

Rivaroxaban is a once daily predictable and dose-dependent inhibitor of factor Xa activity. After oral intake, rivaroxaban is rapidly absorbed. The maximum concentration of rivaroxaban is achieved 2–120 hours after oral intake. To assure a good oral bioavailability, rivaroxaban should be taken together with food. Around two thirds of rivaroxaban undergoes metabolic degradation (50% *via* the kidney and the remaining 50% *via* the fecal route) and about one third is directly excreted by the kidneys. The area under the curve of rivaroxaban progressively increases with renal function decline. Therefore, rivaroxaban 20 mg once daily is the recommended dose in subjects with a creatinine clearance > 50 ml/minute, whereas it should be reduced to 15 mg once daily in subjects with moderate-to-severe renal insufficiency (creatinine clearance of 15–49 ml/minute), and should be avoided in subjects with a creatinine clearance < 15 ml/minute. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant hemorrhagic risk, as in cirrhotic patients with Child–Pugh B and C. However, rivaroxaban can be prescribed in patients with mild hepatic impairment [Salem *et al.* 2015].

The indication for use of rivaroxaban in the prevention of stroke and systemic embolism in patients with NVAF is largely based on the results of the ROCKET-AF trial [Patel *et al.* 2011]; it showed that rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. In fact, after a median follow up of 707 days, rates of stroke or systemic embolism were 1.7% per year with rivaroxaban and 2.2% per year with warfarin (HR 0.79; 95% CI, 0.66–0.96; $p < 0.001$ for non-inferiority). Further, there was no significant between-group difference in the risk of major bleeding (14.9% per year with rivaroxaban and 14.5% per year with warfarin; HR 1.03; 95% CI, 0.96–1.11; $p = 0.44$), although intracranial (0.49 *versus* 0.74 per 100 patient years, HR 0.67; 95% CI, 0.47–0.93; $p = 0.02$) and fatal bleeding (0.2 *versus* 0.5%; $p = 0.003$) occurred less frequently in the rivaroxaban group.

Effectiveness and safety of rivaroxaban in real life

Many studies testing the efficacy and safety of rivaroxaban in clinical practice have been published recently. The Dresden TSOAs Registry [Beyer-Westendorf *et al.* 2014] is a prospective non-interventional registry that included more than 230 physicians from Saxony, Germany. This registry recorded the outcomes and management strategies of 2249 patients receiving target specific oral anticoagulants in 'real-world conditions'. Of these, 1191 patients with NVAF were taking rivaroxaban for stroke and systemic embolism prevention. In this registry, mean $CHADS_2$ score was 2.4; 67.4% of patients received rivaroxaban 20 mg once daily (the remaining 32.6% 15 mg once daily) and 62.8% of patients were naïve to anticoagulant therapy, whereas the rest switched from VKAs to TSOAs, mainly because of poor INR control. Rates of major cardiovascular events were 4.2 events per 100 patient years. However, 28.3% of these events occurred after temporary or

permanent interruption of rivaroxaban. As a result, on-treatment event rate was 3.0 per 100 patient years. Although bleeding complications were common, major bleeding was rare. Only 11.8% of patients withdrew from treatment with rivaroxaban after a 12-month follow up [Beyer-Westendorf *et al.* 2013; Ebertz *et al.* 2013]. The data from the Dresden TSOAs registry showed that rates of rivaroxaban-related major bleeding were lower, whereas the outcome was similar or even better than VKA [Beyer-Westendorf *et al.* 2014]. In summary, the Dresden TSOAs Registry showed that in unselected NVAF patients in daily care, rivaroxaban was effective and safe and was associated with a high treatment adherence.

XANTUS [Camm *et al.* 2015] is the first large, international, prospective study describing the use of rivaroxaban for stroke prevention in a broad NVAF population in the 'real world' clinical practice. This single-arm observational study evaluated the safety and effectiveness of rivaroxaban for stroke prevention in 6784 patients with NVAF enrolled from 311 centers across Europe, Israel and Canada. All treatment and dosage decisions were at the discretion of the treating physicians and the patients were followed at intervals of about 3 months for 1 year or until 30 days after premature discontinuation. The mean follow up was 329 days. A total of 45.5% of the enrolled patients had previously had VKA therapy, while 54.4% were classified as 'naïve' to VKA therapy; 18% had previously had single antiplatelet therapy for stroke prevention (excluding the combination therapies), and 1% had previously had only double antiplatelet therapy. Primary endpoints were: major bleeding, mortality from all causes and all adverse events. Secondary endpoints were: stroke, non-CNS-related systemic embolism, transient ischemic attack, MI and nonmajor bleeding. The bleeding events and major thromboembolic events were centrally adjudicated by an independent committee. The average age was 71.5 years and the average CHA_2DS_2VASc 3.4 (average $CHADS_2$ 2), values closer to those of patients encountered in clinical practice than the population at high risk in the ROCKET study. By the end of the observation period, the majority (96.1%) of patients had not experienced treatment-emergent major bleeding, all-cause death or stroke/systemic embolism. The rate of on-treatment all-cause mortality was 1.9% per year. Overall, 2.1% of patients per year experienced treatment-emergent major bleeding and most of these cases were treated using standard clinical measures. The rate of stroke occurred in 0.7% patients per year, while fatal bleeding was 0.2% per year, critical organ bleeding occurred at a rate of 0.7% per year with 0.4% per year of patients experiencing an intracranial hemorrhage. The causes of death were in about 20% of patients with heart failure, in another 20% with neoplasia and only in 10% with hemorrhage (about 6% intracranial). Patients treated with 15 mg/day rivaroxaban had an increased rate of complications, but this was probably due to their risk characteristics, resulting in choice of the lowest dosage. These results demonstrate low rates of both major bleeding and stroke in patients taking rivaroxaban in routine clinical practice and reaffirm the positive benefit–risk profile of rivaroxaban established in the phase III clinical trial.

In the US, a retrospective study included 2579 AF patients treated with either DAB or rivaroxaban, Fontaine and colleagues showed that only 0.5% of them experienced major bleeding, 0.19% intracranial hemorrhage and 0.08% fatal bleeding [Fontaine *et al.* 2014]. A recent study, aimed at identifying risk factors that increased the risk of hemorrhage with DAB or rivaroxaban in clinical practice through the analysis of available case reports and single case series, found that the main predictors of bleeding were prescriber mistakes, renal insufficiency, concomitant treatment with antiplatelet drugs or P-gp inhibitors, being elderly and low body weight [Pfeilschifter *et al.* 2013]. As a result, these factors identify subgroups at higher risk that should be monitored closely to avoid hemorrhagic events. In a recent observational study [Tamayo *et al.* 2015] using data from a large US Department of Defense electronic-healthcare-records-based cohort of 27,467 NVAF patients treated with rivaroxaban and followed for 15 months, the authors showed that the major bleeding incidence was 2.86 per 100 person years. Major bleeding was most commonly gastrointestinal (88.5%) or intracranial (7.5%). Fatal bleeding was rare. The authors concluded that rivaroxaban is safer than warfarin, as it has been associated with lower risk of fatal and intracranial hemorrhages. By 2015, the rivaroxaban research programme included more than 275,000 patients in clinical trials and the real-world settings across a wide range of treatment settings. It is expected that the real-world evidence will continue to validate rivaroxaban usage in large patient populations across a wide range of risk profiles and comorbidities that reflect everyday clinical practice in order to help

improve patient care [Beyer-Westendorf *et al.* 2016].

Persistence and adherence to rivaroxaban therapy

The Dresden TSOAs Registry showed that only 11.8% of patients withdrew from treatment with rivaroxaban after 12 months of follow up [Beyer-Westendorf *et al.* 2013, 2014; Ebertz *et al.* 2013].

Lalibertè and colleagues found that rivaroxaban was associated with a significantly lower risk of treatment nonpersistence after 6 months' follow up (HR 0.66; 95% CI, 0.60–0.72; $p < 0.0001$). In fact, adherence to rivaroxaban was slightly above 80% after 6 months of treatment [Lalibertè *et al.* 2014]. In a retrospective study aimed at comparing real-world persistence (defined as the absence of refill gap of $>$ 60 days) and discontinuation (defined as no additional refill for at least 90 days and until the end of follow up) among NVAF patients, a significantly higher rate of persistence (aHR: 0.63; 95% CI, 0.59–0.68) and a lower rate of discontinuation (aHR: 0.54; 95% CI, 0.49–0.58) was associated with rivaroxaban therapy compared with warfarin. [Nelson *et al.* 2014].

Recently, the XANTUS trial showed that the majority of patients (80%) persisted on their treatment with rivaroxaban throughout the 1-year study period [Camm *et al.* 2015], whereas other recent data on VKAs has shown a persistence rate of 62% after 1 year [Björck *et al.* 2015].

Conclusion

TSOAs have emerged as an alternative for VKAs for thromboembolic prevention in patients with NVAF. Real-world evidence from several large observational studies and registries support the positive benefit–risk profile of TSOAs that was established in the pivotal phase III clinical trials. The real-world data confirm a better medication adherence and better outcomes in NVAF patients who underwent TSOA therapy. Ongoing large global registries [Huisman *et al.* 2014] will generate further robust data on the use of Novel oral anticoagulants (NOAC) in daily practice.

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