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Review Article

Edoxaban in cardiovascular medicine from scientific evidence to clinical practice

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Abstract

Direct oral anticoagulants have become a reasonable treatment option replacing warfarin in preventing stroke in patients with non-valvular atrial fibrillation and in treating and preventing venous thromboembolism. This article aims to summarize the rationale behind the development of direct oral anticoagulants and to review the key pharmacological properties, clinical and reallife data of the factor Xa inhibitor edoxaban, that may contribute to improving patient outcomes in cardiovascular clinical practice.

Keywords: Edoxaban, atrial fibrillation, venous thromboembolism, deep vein thrombosis, direct oral anticoagulants

INTRODUCTION

"The practice of medicine is an art based on science."

Sir William Osler

In his famous quote above [1], William Osler drew attention to the importance of science in the practice of medicine more than a century before the concept of "evidence-based medicine" emerged [2]. Advances in research have evolved the body of scientific knowledge and changed the diagnostic process and therapeutic approach for many disorders over time. Venous thromboembolism (VTE) and stroke are among the most burdensome, challenging and frequently encountered vascular conditions in clinical practice [3,4], where significant improvements have occurred within the last 100 years [5].

Given the high recurrence, morbidity, and mortality rates, long-term anticoagulation, "for an indefinite period" in some group of patients, is required for effective management of arterial and venous thromboembolic events [6-8]. Therefore, the introduction

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of vitamin K antagonists (VKAs) as oral anticoagulant treatment options suitable for long-term use [5,9], is considered to be a landmark in medicine [10]. Direct oral anticoagulants (DOAC) are also referred to as NOACs standing for Non-Vitamin K Antagonist Oral Anticoagulants (or New Oral Anticoagulants, initially) [11]. The DOACs comprise the Factor IIa inhibitor, dabigatran, and the Factor Xa inhibitors, namely rivaroxaban, apixaban and edoxaban [5].

This article aims to provide a clinical perspective on edoxaban use in cardiovascular practice by reviewing the rationale behind the development of DOACs and the key findings from the clinical and real-world studies of edoxaban, the latest DOAC approved for stroke prevention in atrial fibrillation (SPAF) and treatment and prevention of VTE.

Rationale behind the development of DOACs

VKAs have been the key oral anticoagulants for preventing and treating VTE as well as preventing SPAF for decades [5,12]. They have a well-established efficacy in reducing clot formation but pose a significant bleeding risk, which can be life-threatening or fatal, especially in patients with predisposing factors [12]. The development of warfarin which had long been the preferred oral anticoagulant is an excellent example of the "thin red line" between a drug and a poison, anecdotally explaining the increased bleeding risk associated with VKAs. In the early 20th century, veterinarians in Canada and the Northern United States of America observed that cattle fed with mouldy sweet clover hay died of internal bleeding. The American biochemist Karl Link studied this hemorrhagic phenomenon and showed that vitamin K1 reversed the effects of dicoumarol which he had extracted from mouldy sweet clover. His persistent efforts led to the discovery of warfarin, a stronger anticoagulant named after the initials of the Wisconsin Alumni Research Foundation (WARF) which supported Link's research, and the suffix 'arin' of the natural product coumarin [13]. Warfarin was first marketed as a rodenticide in 1948 and approved as a human medicinal product in 1954. Its popularity has increased after its use by the US President Dwight Eisenhower following the heart attack, he experienced in 1955 [14].

VKAs have a narrow therapeutic index which mandates frequent monitorization of International Normalized Ratio (INR) and dose adjustment [15]. It is noteworthy to emphasize that even if INR is within the therapeutic window, poor time in therapeutic range (a TTR below <65% [ideally70%]) can increase the bleeding or stroke risk in patients treated with VKAs [16]. Slow initiation and termination of VKAs action and interactions with food and drugs also complicate their use in clinical practice [15].

Discovery of clotting factors and understanding of their sequential activation in the coagulation cascade prompted the research on new medications that could potentially overcome the disadvantages of VKAs and paved the way for development of DOACs. Dabigatran has been the first DOAC in the market (EU: 2008 [17] and US: 2010 [5]) followed by rivaroxaban which was launched in 2011 [5].

Unlike VKAs, DOACs have a predictable pharmacological profile and fewer interactions with food and drugs. Therefore, INR is not routinely measured and frequent dose adjustments are not required in most patients on DOACs [5]. Clinical trials have shown that DOACs have at least a comparable efficacy to VKAs in terms of stroke prevention in non-valvular atrial fibrillation (NVAF) [18-21] and treatment and prevention of VTE [22-26]. The bleeding risk with DOACs is lower than that of VKAs [18-26]. Based on these findings, they have become a reasonable alternative to VKAs in their approved indications and their use in both VKA naïve and VKA experienced patients is expanding.

Edoxaban

Edoxaban is a rapid, selective, orally bioavailable, direct acting factor Xa inhibitor suitable for once daily use [27,28]. It reduces generation of thrombin and thrombus formation by preventing the interaction of factor Xa with prothrombin [29].

The name edoxaban is derived from the union of “Edo”, the former name of Tokyo and the suffix “Xaban” that represents the direct factor Xa inhibitors [30].

The initial approval of edoxaban for prevention of ischemic stroke and systemic embolism in NVAF and for treatment and prevention of VTE was granted by the the Japanese health authority, in 2014 [31]. Edoxaban is approved for these indications in numerous countries including the US and the EU countries where it has been available since 2015 [32,33]. It is approved and reimbursed in Turkey since end of 2017 [34].

Edoxaban is rapidly absorbed following oral intake and its highest plasma concentration is achieved within 1-2 hours. The absolute oral bioavailability for a 60 mg dose is approximately 62% [35]. Its terminal half-life is 10-14 hours and renal excretion constitutes 50% of its total clearance. Given the linear and predictable pharmacological characteristics of edoxaban, the bioavailability results are applicable to 30 mg dose and routine monitoring of coagulation parameters is not required during treatment with edoxaban [36].

Food augments maximum exposure to edoxaban however its impact on overall systemic exposure is negligible [33,34]. Edoxaban tablets can be received either intact or crushed. Administration through a nasogastric tube after suspending the crushed tablet in a small amount of water is also possible [34].

Edoxaban is recommended at a dose of 60 mg taken once daily

(od) except under the following conditions which mandate a dose reduction to 30 mg od: Presence of moderate to severe decline in kidney function (i.e. a creatinine clearance (CrCl) value of 15 - 50 mL/min according to Cockcroft-Gault formula), a body weight lower than or equal to 60 kg or intake of edoxaban together with strong P-glycoprotein (P-gp) inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole requires a dose reduction to 30 mg. It is noteworthy to underline that concomitant use of several P-gp inhibitors commonly prescribed in cardiovascular practice such as amiodarone, quinidine, and verapamil does not require a decrease in edoxaban dose [34].

Unlike rivaroxaban and apixaban, significant fractions of which are metabolized via CYP3A4/5 pathway (~15% for apixaban and ~18% for rivaroxaban), less than 4% of total edoxaban dose is metabolized by this enzyme system [8,37]. Clinically meaningful drug-drug interactions via cytochrome P450 (CYP) pathway are less likely to occur with edoxaban [8,38].

According to the European Heart Rhythm Association Practical Guide on the Use of NonVitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation (EHRA) 2021, edoxaban (also apixaban) may be preferred for anticoagulation in the presence of severe renal insufficiency (CrCl of 15–29 mL/min) considering its phase 3 data and dose reduction criteria [8]. Although no dose adjustment for edoxaban is needed in case of mild to moderate decline in liver function (i.e. Child-Pugh A and B), the drug still needs to be used cautiously in patients with ALT/AST > 2x ULN (upper limit of normal) or total bilirubin ≥ 1.5 x ULN [34].

AF and stroke are associated with dementia [39,40]. Twice daily regimens and dementia have been shown to impair the adherence to DOACs [41]. The EHRA 2021 guide reports that once daily medications such as edoxaban as well as weekly boxes, blister packs and date/time of administration reminders can help improve adherence in these patients [8].

Indications of edoxaban

Stroke prevention in atrial fibrillation (SPAF)

Stroke is a global health concern which results in substantial disability and mortality. In 2019, it was the second leading cause of overall deaths (11.6%) and the third most common cause of disability-adjusted life-years (DALYs) (5.7%) [42]. AF is the most frequently encountered heart rhythm abnormality; its estimated prevalence is reported to be 1 to 4% in the US, Europe and Australia and varies between 0.49% to 1.9% in Asia [43]. The risk of ischemic stroke is 3 to 5fold higher in AF than in general population [44]. AF-related strokes are more disabling and have higher recurrence and death rates than non-AF-related ones [45].

The efficacy of edoxaban versus warfarin for prevention of stroke or systemic embolism in subjects with NVAF was demonstrated in the pivotal ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) study which is the largest (n=21.105) and longest (median duration 2.8 years) comparative SPAF study to date [21]. The mean CHADS2 score of the study population was 2.8± 0.1 indicating a moderate to high risk of stroke and the median TTR in the warfarin arm was 68.4% (IQR [interquartile range]: 56.5-77.4) of the treatment period. The annualized rates of stroke or systemic embolic event (S/SEE) were 1.50%, 1.18% and 1.61% with warfarin, edoxaban 60 mg od and 30 mg od, respectively, demonstrating that edoxaban was as effective as warfarin regarding to prevention of S/SEEs (for non-inferiority HR:0.79; 97.5%CI:0.63-0.99; p<0.001 for edoxaban 60 mg vs warfarin and HR:1.07; 97.5%CI:0.87-1.31; p=0.005 for edoxaban 30 mg vs warfarin). Edoxaban reduced both annualized mortality and cardiovascular mortality compared to warfarin. Additionally, the annualized rates of major, life-threatening, intracranial, and major plus clinically relevant non-major (CRNM) bleedings were lower with edoxaban than with warfarin (p<0.001 for all comparisons). On the other hand, compared to warfarin, edoxaban 60mg was associated with higher rates of major gastrointestinal bleedings (1.51% vs 1.23%, HR:1.23; 95%CI:1.02-1.50; p=0.03) but major gastrointestinal bleedings occurred less commonly in the edoxaban 30 mg arm than in the warfarin arm (0.82% vs 1.23%, HR:0.67; 95%CI:0.53-0.83; p<0.001) [21].

Various post-hoc and subgroup analyses were performed on ENGAGE AF–TIMI 48 data to further investigate the comparative efficacy and safety of edoxaban versus warfarin in clinical conditions that can influence the course of disease and/or the treatment outcomes [46-51]. These analyses broadly revealed that, in patients with NVAF, edoxaban remained to display a comparable efficacy and a better safety profile versus warfarin in many challenging clinical conditions such as moderate-to-severe valvular heart disease (VHD) excluding mitral stenosis or mechanical heart valves [46], diabetes mellitus [47], and extremely low (below 55 kg; <5 percentile) or high (>120 kg; >95 percentile) body weights [48]. It was also shown that edoxaban (60 mg or 30 mg od) significantly reduced the net clinical outcome (NCO) which was a composite endpoint that included stroke/SEE, major bleeding, or death) versus warfarin in many high-risk patient subgroups: elderly (≥75 years old), Asian origin, moderately disturbed kidney function (CrCl ≤50mL/min), prior stroke/transient ischemic attack, body weight <55 kg (compared to 79.8-84 kg), concomitant single antiplatelet drug use, and VKA-naïve [49]. Based on the consistent efficacy and safety of edoxaban compared to warfarin in patients with low body weights, the EHRA 2021 guide reported that it is a suitable treatment option for individuals weighing ≤60kg [8].

The ENGAGE AF-TIMI 48 study also pointed out that edoxaban remained to be safer and more efficacious than warfarin irrespective of the burden of concomitant disease evaluated with the Updated Charlson Comorbidity Index (CCI) but the outcomes were worse in subjects with higher CCI scores.[50] In a pre-specified analysis of the ENGAGE AF–TIMI 48 study, edoxaban significantly reduced the risk of severe bleeding and deaths compared to warfarin, irrespective of risk of falling but its beneficial effects were enhanced in patients at increased risk of falling [51]. These findings were specifically mentioned in the EHRA 2021 guideline [8].

The results of the analyses summarized above confirms that edoxaban is a viable treatment option for patients with AF in real-life and support its use in a wide spectrum of patients in daily practice. Accordingly, real-world data on the outcomes achieved with edoxaban in SPAF have been increasing. ETNA-AF (Edoxaban Treatment in routiNe clinical prActice in Patients with nonvalvular Atrial Fibrillation) is a large (targeting >26.000 patients), global, non-interventional, post-authorization program complementing the findings from the ENGAGE AF-TIMI trial; it includes AF patients treated with edoxaban in real-life [52]. The 1-year results of the global ETNAAF program (n=26.823) revealed that the study population represented a broader range of patient characteristics than ENGAGE AF-TIMI 48 [53]. Patients included in this analysis had a median age of 75 (IQR: 68 - 80) years; their median (IQR) CHA2DS2 -VASc and HAS-BLED scores were 3.0 (2.0 - 4.0) and 2.0 (2.0 - 3.0), respectively, at baseline. Most patients (82.6%) received the appropriate dose of edoxaban. Given the potential harmful effects of over/ under utilization, this result is very valuable in terms of both the effectiveness and safety of the drug. Stroke and bleeding events were rarely observed; the rate of ischemic stroke was 0.87%/year and that of major bleeding was 1.12%/year (0.31%/ year for intracranial hemorrhage and 0.57%/year for major gastrointestinal [GI] bleeding). Cardiovascular deaths occurred at a rate of 1.22%/year and constituted 40% of all deaths (3.03%/ year) [53]. The ETNA-AF-Europe results at 2-year follow up (n=14.317) [54] and those of the recently published Dresden NOAC Registry) (n>5000 of whom 1258 were treated with ; 2.5 years follow up) [55] were consistent with each other and further supported the beneficial effects of edoxaban use in AF.

To the best of our knowledge, the ongoing, prospective, observational ETAF-TR (The Evaluation of Treatment Safety in Patients with Atrial Fibrillation on Edoxaban Therapy in Real-Life in Turkey) study is the first study evaluating the outcomes associated with edoxaban use in daily practice in Turkey [56]. The study will primarily evaluate overt bleedings which include major/ CRNM bleedings as well as any other bleedings judged by the treating physician as overt bleeding. In addition, the study will also examine the treatment persistence, and posology of edoxaban in cardiovascular practice [56].

Recent clinical guidelines recommend oral anticoagulation with DOACs instead of VKAs for prevention of stroke in patients with NVAF [6,7]. Since no head-to-head controlled studies comparing DOACs have been conducted so far, it is inappropriate to draw conclusions about the superiority of one DOAC over another. For now, clinicians should consider the availability, prescribing information and accessibility of DOACs, and, more importantly, individual patient characteristics when deciding which DOAC to prescribe to their patients.

Treatment of VTE

Venous Tromboembolism is the third most prevalent acute cardiovascular condition preceded by myocardial infarct and stroke. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two clinical presentations of the disease [4]. It tends to recur in 30% of patients within 10 years of the initial event. [57]. Anticoagulation is the cornerstone of VTE management. Its purpose is both to treat the acute episode and to prevent the recurrent events. Accordingly, a 3-phase management approach is recommended: an initiation phase (up to 10 days [5-21 days according to CHEST guidelines] after diagnosis) to rapidly induce anticoagulation to treat the acute event and prevent its spread, a principal treatment phase (3 months) aimed at preventing early recurrences by maintaining anticoagulation, and an extended treatment phase (beyond 3 months) for secondary prevention [6,58,59]. Many of the detrimental outcomes associated with VTE, including death, can be avoided with appropriate management.

DOACs are effective in management of both provoked and unprovoked DVT; they remarkably decrease the risk of major bleeding and they are recommended instead of VKAs by recent

guidelines for principal and extended treatment of VTE [6,58,59]. They eliminated the need for hospitalization for the treatment of uncomplicated DVT [6]. Selection of the suitable anticoagulant agent for the treatment phase of VTE requires meticulous assessment of individual patient characteristics such as kidney function, bleeding risk, adherence to treatment; drug availability and accessibility, and patient preferences [6]. The standard approach to VTE management is to discontinue anticoagulation after three to six months in patients not at risk for recurrent events. The decision for longer-term treatment should be evaluated on an individual basis [6,58,59]. Although the risk of recurrence in provoked DVT is lower than in unprovoked DVT, it should not be ignored. Iorio et al., in a systematic review, reported that the risk of recurrent VTE after a provoked DVT was 3.3%/patient-year two years after stopping anticoagulation and 0.7% if the provoking factor was surgical intervention. [60] The European Society for Vascular Surgery (ESVS) 2021

Clinical Practice Guidelines on the Management of Venous Thrombosis recommend 3 months of anticoagulation for DVT provoked by a major transient risk factor including surgery, short term confinement to bed or reduced mobility. For recurrent VTE, pulmonary embolism, unprovoked events, or events provoked by a minor transient risk factor, anticoagulation is suggested for at least 3 months. Risk of thrombosis and bleeding and patient preferences should be considered while making treatment decision. Since patients with an underlying active cancer, severe thrombophilia, or chronic rheumatic diseases have an increased risk of recurrent VTE, they should not discontinue anticoagulant therapy unless contraindicated [58].

Edoxaban, which was previously recommended as an option for the principal treatment phase in VTE following initial use of heparin or low molecular weight heparin (LMWH), has been named among the long-term treatment (>3 months) alternatives for VTE in the 2021 versions of many guidelines based on the current scientific evidence [6,8,58,59].

HOKUSAI-VTE is the pivotal, 12-month study demonstrating the efficacy and safety of edoxaban versus warfarin in VTE [61]. The study included 8292 adults who presented with acute, symptomatic distal DVT or PE (±DVT) and received edoxaban (60 mg or 30 mg od, in line with dose reduction criteria) or warfarin for 3 to 12 months following an initial enoxaparin or unfractioned heparin treatment of at least 5 days. The incidences of recurrent symptomatic VTE (primary efficacy outcome) in the edoxaban (3.2%) and warfarin (3.5%) arms were comparable (HR:0.89; 95%CI:0.70-1.13; p<0.001 for non-inferiority). The percentage of patients who died was 5.5% in each group (HR:1.00; 95% CI:0.83-1.20). The percentage of patients who had major or CRNM bleeding was approximately 20% lower in the edoxaban arm (8.5%) compared to warfarin arm (10.3%) (HR: 0.81; 95%CI:0.71-0.94; p=0.004 for superiority). The incidences of any bleeding (21.7% vs 25.6%; HR:0.82, 95%CI:0.75-0.90; p<0.001) and CRNM bleeding were also lower with edoxaban (7.2% vs 8.9, HR:0.80, 95%CI:0.68-0.93; p=0.004). The groups were comparable regarding major bleeding (1.4% in edoxaban vs 1.6% in warfarin arms; HR:0.84, 95%CI:0.59–1.21; p=0.35) [61].

Several sub-group and post-hoc analyses of HOKUSAI-VTE have been performed to better delineate the efficacy and safety profile of edoxaban in various patient groups.[62-66] Extended treatment with edoxaban (>3 months) decreased the risk of recurrent VTE by 22% compared to warfarin.[62] Edoxaban remained to be more efficacious and at least as safe as warfarin in elderly patients (≥75years) and in patients having multiple comorbidities despite the increase in bleeding rates with age, comorbidities, and polypharmacy [63]. Di Nisio et al. identified female gender, antiplatelet drug use, hemoglobin level ≤10 g/dl, history of hypertension and systolic blood pressure >160 mm/Hg as main factors associated with the increased risk of major and CRNM bleeding in patients acute VTE treated with either edoxaban or warfarin [64]. A pre-specified subgroup analysis of the HOKUSAI-VTE focused on patients with PE and right ventricular dysfunction revealed that edoxaban was superior to warfarin in preventing recurrent VTE (3% vs 6%, HR:0.50; 95%CI:0.26-0.94; p=0.033) in patients with NT-proBNP level≥500 pg/ml and it was at least as effective (3%) as warfarin (5%) (HR:0.57; 95%CI:0.27-1.17; p=0.13) in patients with right/left ventricular diameter ratio ≥0.9 [65].

The comparative efficacy and safety of reduced edoxaban dose (30 mg od) versus warfarin was also investigated in the HOKUSAI-VTE study [61]. These results demonstrated that the efficacy of edoxaban in preventing recurrent VTE as well as its safety regarding bleeding events were maintained in subjects fulfilling the dose reduction criteria [61]. Additionally, Verhamme et al. reported that both doses of edoxaban were comparable in reducing recurrent VTE and clinically significant bleeding (VTE recurrence: 3% vs 3.2%; clinically relevant bleeding rate: 7.9% vs 8.9% in 30 and 60 mg doses, respectively). Furthermore, they found that edoxaban 30 mg was safer than warfarin (VTE recurrence: 4.2%; bleeding rate: 12.8%) in patients with VTE who were eligible for dose reduction [66].

Several studies explored the outcomes of patients who received edoxaban for VTE in clinical practice. ETNA-VTE (Edoxaban Treatment in routiNe clinical prActice in patients with Venous ThromboEmbolism) is a prospective, multinational, observational study program that evaluates the effectiveness and safety of edoxaban in >4500 patients with VTE in real-life [52]. The comparison of the European cohorts of ETNA-VTE and HOKUSAI-VTE studies revealed that edoxaban was used in an older (65 vs 57 years) patient population with lower CrCl (≤50 ml/min 10.2 % vs 4.1%) and body weight (<60 kg:9.3% vs 5.6%), and a higher percentage of women (46.5% vs 39.8%) in routine clinical practice [67]. Edoxaban was appropriately dosed in the majority of cases (90%) and anticoagulation with heparin preceeded edoxaban treatment in 84.7% of patients [67]. An interim analysis of the ETNA-VTE Europe study (n=2672; DVT-only: 58.2%; PE only: 22.2%; DVT+PE:19.6%) showed that the rates of recurrent VTE (0.34%), major bleeding (0.97%) and deaths (0.79%) were low with edoxaban during the first 3 months of treatment, when the risk of recurrent VTE was highest [68]. Major bleeding (1.9%) and VTE recurrence (2.83%) rates at 12 month were also reported to be low [69]. Similarly, the incidences of major bleeding (2.6%) and recurrent VTE (1.8%) over 12 months were low in ETNA-VTE Japan (n=1732; DVT-only: 57.4%; PE ±DVT 42.3%) study [70]. Considering potential impact of obesity on the distribution and half-life of DOACs thereby worsening treatment outcomes, Schindewolf et al.

analyzed the impact of body mass index (BMI) on the outcomes in the ETNAVTE-Europe study and reported that obesity had no effect on VTE recurrence in patients treated with edoxaban [71]. Bleeding risk evaluated with VTE-BLEED score (<2 and ≥2) which included active cancer, uncontrolled hypertension, male gender, anemia, history of major or CRNM bleeding, age >60, and renal dysfunction (CrCl< 60 ml/min) also did not have an impact on the effectiveness of edoxaban in reducing recurrent VTE at 12 month in the ETNA-VTE-Global study but the mortality rates and bleeding incidences were higher in the patients with high VTEBLEED scores [72]. A prospective analysis of the Dresden DOAC registry reported 891 bleeding events in 996 patients treated with edoxaban for SPAF or treatment of VTE (minor: 53.2%, CRNM: 41.9%, major: 4.9%)[73]. Authors reported that the rate of major bleeding associated with edoxaban use was consistent with those reported in the phase 3 trials and there was no difference between edoxaban and other DOACs regarding bleeding patterns, management, and outcomes [73]. In 2021, Bavalia et al. published the quality of life results of 251 patients treated with edoxaban or warfarin for PE in the Hokusai-VTE trial at 7 years after randomization. In this single visit study, the authors observed no difference in QoL between the two groups based on the 36-item Short Form Health Questionnaire (SF-36) and Pulmonary Embolism Quality of Life Questionnaire (PEMB-QOL) scores [74].

An interesting review of 51 articles published until 2019 in terms of treatment failure rates of DOACs showed that 30.4% and 6.3% of failures (n=79; 51.6% male, mean age: 52.8 years) occurred in patients with AF and DVT, respectively. Failure rate was highest with rivaroxaban (65.8%) followed by dabigatran (27.8%), apixaban (7.6%) and edoxaban (1.3%). DOACs also differed regarding the median time to failure: dabigatran (126 days), rivaroxaban (90 days), and edoxaban (60 days) and apixaban (8 days). More than half of patients were switched to VKAs following failure [75].

Untreated distal DVTs (DDVT) have a >10% risk of propagation to the popliteal or femoral vein and/or PE.[76] Most guidelines, including CHEST 2021, ESVS 2021, and Turkish National Treatment Guideline for peripheral Arterial and Venous Diseases 2021[6,58,59] recommend a 3- month anticoagulation therapy for DDVT if patients are symptomatic or at high risk of proximal propagation. It has been reported that the risk of recurrent VTE after unprovoked DVT is 7.4%/patient-year two years after stopping anticoagulation.[60] In the ESVS 2021 Guidelines, a direct DOAC is recommended (class 1A) rather than a VKA for the first 3 months of an unprovoked DVT.[58] The CHEST 2021 and the Turkish National Guidelines 2021 strongly recommend prolonged anticoagulation with a DOAC for unprovoked DVT or VTE provoked by a persistent risk factor. Alternatively, VKA can be used by patients who are unable to use DOACs [6,59].

In 2022, Pham et al. reported the findings from the TriNetX healthcare database which included 6509 patients treated with a VKA or a DOAC for the treatment of DDVT. They observed that the the incidences of PE (1.80% vs 3.60%; p=0.0020) and major bleeding (7.95% vs 10.51%; p = 0.0134) were lower with DOAC treatment than warfarin [77].

Anticoagulation in patients with cardiovascular surgical interventions

Pre-existing or new onset AF is a commonly observed comorbidity in patients who have undergone transcatheter aortic valve replacement (TAVR) [78]. The multicenter, prospective, randomized, open-label (with blinded end point) ENVISAGE TAVI AF trial compared edoxaban (n=713) with VKAs (n=713) in NVAF patients for whom oral anticoagulation is indicated for AF after a successful TAVI [79]. Edoxaban and VKAs were comparable regarding the primary outcome of net adverse clinical events (NACE) which were a composite of all-cause mortality, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding [79]. The rates of NACE in edoxaban and VKA arms were 17.3%/year and 16.5%/year, respectively (HR:1.05; 95%CI:0.85-1.31; p=0.01 for non-inferiority). However, major bleeding risk was greater in the edoxaban arm mainly due to high GI bleeding rates in this group [79]. Due to the paucity of scientific data and the presence of confounding factors in observational studies, there is not a clear recommendation about the use of DOACs after TAVR [7,8]. The treatment decision should therefore be individualized, considering patient's bleeding and thrombotic risk. Since new onset AF is a frequent complication of cardiac surgery, Sezai et al, in a pilot study, observed 15 patients who developed AF after cardiac surgery and were given edoxaban for 2 months and did not observe any cerebrovascular event or bleeding [80]. A prospective, observational study comparing the effectiveness and safety of DOACs in post-operative AF also supported the favorable profile of edoxaban in real-life [81].

In a recent systematic review and meta-analysis of 12 studies which included patients who had AF after cardiac surgery and were treated with DOACs (n=8587) or warfarin (n=8315), DOACs were more effective in reducing neurological events (RR:0.63; 95%CI:0.48-0.83; p=0.0012) and safer in terms of bleeding risk (RR:0.74; 95% CI: 0.62-0.89; p=0.0011) than warfarin, but the treatments were comparable regarding mortality risk (RR:1.02; 95% CI:0.77-1.35; p=0.090) [82]. Endovascular interventions have gained importance in recent years for the treatment of DVT due to their potential contribution to preventing post-thrombotic syndrome [83-85]. The rationale behind endovascular treatment of acute DVT is the early and complete removal of thrombus restoring blood flow and preserving vein walls and vessels thereby preventing residual obstruction and venous hypertension.

Catheter directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT) and pharmacomechanical catheter directed thrombolysis (PCDT) can be performed for this purpose [83-85]. The risk of bleeding is the main problem associated with thrombolysis. The absolute contraindications for thrombolysis include previous hemorrhagic stroke, intracranial disease, active non-menstrual bleeding, ischemic stroke within three months prior to thrombolysis, tendency to bleed and cerebral tumor [59]. The studies about catheter-directed pharmacomechanical thrombolysis have controversial results. While the CAVENT study reported positive results [86], the ATTRACT and CAVA studies could not show a significant benefit [87,88]. In recent guidelines, including the Turkish National guidelines on the management of VTE, these treatment modalities are recommended for use in selected patients such as a young patient with a low risk of bleeding, or with phlegmasia cerulea dolens, or symptomatic DVT in the iliac and common femoral veins [58,59]. A significant number of patients need venous stenting especially for proximal occlusive lesions; there are controversies about the optimal anticoagulation regimen in these patients. Patients treated with pharmacomechanical intervention for DVT should initiate and continue anticoagulation in the same way as patients without early thrombus removal. The anticoagulant should be chosen at the discretion of the treating physician, taking into account the individual patient characteristics. The suggested duration of treatment is the same as in patients taking anticoagulants alone. A "tailor-made" anticoagulant treatment selected based on the judgement of the treating physician is recommended for patients with iliofemoral DVT in whom an early thrombus removal intervention was performed. Patient monitorization and follow up must be planned individually [58,59].

The prospective, observational, multinational EMIT-AF/VTE (Edoxaban Management In diagnostic and Therapeutic procedures-AF/VTE) study evaluated the periprocedural management and outcomes of patients who underwent various diagnostic and therapeutic procedures (95.2% elective: 434 transcatheter vascular, 136 cardiothoracic and vascular, 127 dental and 117 gastrointestinal) and anticoagulated with edoxaban (n=1155) (92.2% of whom treated for AF) [89]. Overall, the risks of periprocedural bleeding and acute thromboembolic event were low; 5 major and 8 CRNM bleedings, 5 deaths, 7 acute thromboembolic events including 2 cardiovascular deaths and 1 acute coronary syndrome (ACS) occurred during the 35-day observation period (starting from fifth day before procedure). Importantly, the authors drew attention to two points that may have clinically important implications: first, 9.5% and 7% of patients were underdosed and overdosed, respectively; secondly, contrary to EHRA recommendations, edoxaban was unnecessarily interrupted in 23.8% of minor-risk patients, while it was not interrupted in 42.1% of low- or high-risk patients as needed, during the periprocedural period [89].

Cancer-associated Venous Thrombosis (CAVT)

Malignancy is a well-known risk factor for VTE associated with 3 to 7-fold rise; VTE incidence can be as high as 10-20% in cancer patients and thromboembolic events show a high tendency to recur [90]. The guidelines on VTE management updated after 2020 include all factor Xa inhibitors among treatment options for CAVT [6,58,59,91]. However, there are some differences between the recommendations of the guidelines on factor Xa inhibitor use. While the CHEST 2021 guideline strongly recommends a factor Xa inhibitor over LMWH for both the initiation and treatment phases of therapy [6], the American Society of Hematology (ASH) 2021 guideline for management of VTE in patients with cancer recommends an initial therapy with LMWH and suggests the use of factor Xa inhibitors for short-term (3-6 months) treatment of CAVT over LMWH or VKA [91]. The guideline also suggests an extended treatment for secondary prophylaxis. On the other hand, the ESVS 2021 guideline, with a more conservative approach, recommends using LMWH in initial and principal phases of cancer associated VTE treatment and switching to an oral anticoagulant after 3-6 months for extended treatment [58]. The guideline further states that an approved DOAC should be considered at all treatment phases (edoxaban for principal and extended phases) except in patients with gastrointestinal or genitourinary tumors [58]. Physicians should consider the absolute and relative contraindications for anticoagulation before making treatment decision. Prior to treatment with DOAC, patients should be carefully evaluated for factors which may affect the effectiveness, safety, and tolerability of the drug including but not limited to nausea, vomiting, potential drug-drug interactions [especially via P-gp or CYP3A4], impaired liver and kidney function, tumor location, and risk of bleeding, Analysis of cancer subgroup in the HOKUSAI-VTE and findings from the HOKUSAI-VTE Cancer trial which was specifically conducted in patients with CAVT provided data about efficacy and safety of edoxaban in this condition.[92,93] In the CAVT subgroup of HOKUSAI-VTE (n=733), recurrence rates of VTE with edoxaban (4%) and warfarin (7%) were comparable (HR:0.53, 95%CI:0.28-1.00; p=0.0007) and the risk of clinically relevant bleeding was lower by 36% in the edoxaban arm (12% vs 19%; HR:0.64; 95%CI:0.45-0.92; p= 0.017) [92].

The multinational, prospective, randomized, open-label, blinded endpoint evaluation (PROBE)

HOKUSAI-VTE Cancer study (n=1512) compared edoxaban (≥6 months to 12 months) with the standard of care (LMWH) for CAVT and showed that, in terms of the composite outcome of recurrent VTE or major bleeding, edoxaban was comparable (12.8%) to dalteparin (13.5%) (HR:0.97; 95%CI:0.70-1.36; p=0.006 for non-inferiority) [93]. Recurrent VTE occurred in a numerically lower percentage of patients in edoxaban arm (7.9%)

than in dalteparin arm (11.3%) (p=0.09). Major bleeding occured more commonly in patients who received edoxaban (6.9% vs 4.0%; p=0.04) because of the increased risk of bleeding with this agent in patients with gastrointestinal cancer [93].

Findings from real-world studies conducted on patients with various types of cancers experiencing VTE are broadly consistent with the findings from the randomized controlled studies [94,95], and support the acceptability of edoxaban as a treatment option for treating VTE and preventing recurrent events in properly selected cancer patients.

In this article, we overviewed the outcomes with edoxaban in various settings based on scientific data gathered from clinical and real-life studies. The consistent efficacy and safety of edoxaban in a wide range of patients with NVAF or VTE suggest that it is a reliable treatment option to prevent and treat tromboembolism. An individualized treatment and follow-up plan will contribute to achieving optimal clinical outcomes.

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