Edoxaban versus Warfarin in high-risk patients with atrial fibrillation: A comprehensive analysis of high-risk subgroups

Gencer, Baris; Eisen, Alon; Berger, David; Nordio, Francesco; Murphy, Sabina A; Grip, Laura T; Chen, Cathy; Lanz, Hans; Ruff, Christian T; Antman, Elliott M; Braunwald, Eugene; Giugliano, Robert P

How to cite

GENCER, Baris et al. Edoxaban versus Warfarin in high-risk patients with atrial fibrillation: A comprehensive analysis of high-risk subgroups. In: The American heart journal, 2022, vol. 247, p. 24–32. doi: 10.1016/j.ahj.2021.12.017

This publication URL: https://archive-ouverte.unige.ch/unige:161743

Publication DOI: 10.1016/j.ahj.2021.12.017

Edoxaban versus Warfarin in high-risk patients with atrial fibrillation: A comprehensive analysis of high-risk subgroups

Baris Gencer, MD, MPH[a,b,c], Alon Eisen, MD[d], David Berger, MD[d], Francesco Nordio, PhD[a], Sabina A. Murphy, MPH[a], Laura T. Grip, MSc[a], Cathy Chen, MD[e], Hans Lanz, MD[f], Christian T. Ruff, MD, MPH[a], Elliott M Antman, MD[a], Eugene Braunwald, MD[a], and Robert P Giugliano, MD, SM[a] ***Boston, MA; Geneva, Switzerland***

Background To compare the efficacy and safety of edoxaban vs warfarin in high-risk subgroups.

Methods ENGAGE AF-TIMI 48 was a multicenter randomized, double-blind, controlled trial in 21,105 patients with atrial fibrillation (AF) within 12 months and $CHADS_2$ score $\geq$2 randomized to higher-dose edoxaban regimen (HDER) 60 mg/reduced 30 mg, lower-dose edoxaban regimen (LDER) 30 mg/reduced 15 mg, or warfarin, and followed for 2.8 years (median). The primary outcome for this analysis was the net clinical outcome (NCO), a composite of stroke/systemic embolism events, major bleeding, or death. Multivariable risk-stratification analysis was used to categorize patients by the number of high-risk features.

Results The annualized NCO rates in the warfarin arm were highest in patients with malignancy (19.2%), increased fall risk (14.0%), and very-low body weight (13.5%). The NCO rates increased with the numbers of high-risk factors in the warfarin arm: 4.5%, 7.2%, 9.9% and 14.6% in patients with 0 to 1, 2, 3, and $\geq$4 risk factors, respectively (P_{trend} <0.001). Versus warfarin, HDER was associated with significant reductions of NCO in most of the subgroups: elderly, patients with moderate renal dysfunction, prior stroke/TIA, of Asian race, very-low body weight, concomitant single antiplatelet therapy, and VKA-naïve. With more high-risk features (0->4+), the absolute risk reductions favoring edoxaban over warfarin increased: 0.3%->2.0% for HDER; 0.4%->3.4% for LDER vs warfarin ($P = .065$ and $P < .001$, respectively).

Conclusions While underuse of anticoagulation in high-risk patients with AF remains common, substitution of effective and safer alternatives to warfarin, such as edoxaban, represents an opportunity to improve clinical outcomes. (Am Heart J 2022;247:24–32.)

Edoxaban is one of 4 approved direct oral anticoagulants (DOACs) for the prevention of stroke and systemic embolism events (SEE) in patients with atrial fibrillation (AF).[1] The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was the largest (21,105 patients) and longest (median 2.8 year follow-up) randomized clinical trial comparing the efficacy and safety of a DOAC with warfarin in patients with AF (56,346 patient-years of observation).[2,3] Patients were randomized to once daily warfarin (target INR of 2.0-3.0), higher-dose edoxaban regimen (HDER) 60 mg, or lower-dose edoxaban regimen (LDER) 30 mg. For patients in either edoxaban arm, the dose was reduced by half for creatinine clearance (CrCl) $\leq$50 mL/min, weight $\leq$ 60 kg, or concomitant potent P-glycoprotein inhibitor. The prespecified primary end point for this analysis was the net clinical outcome (NCO), defined as the composite of stroke/SEE, major bleeding or all-cause death.[2,3]

From the [a]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, and Department of Medicine, Harvard Medical School, Boston, MA, [b]Cardiology Division, Geneva University Hospitals, Geneva, Switzerland, [c]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, [d]Cardiology Department, Rabin Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [e]Daiichi Sankyo Inc , Banking Ridge, NJ, [f]Daiichi Sankyo Europe GmbH, Munich, Germany

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CrCl, creatinine clearance; CI, confidence intervals; DOAC, direct oral anticoagulant; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; HDER, higher-dose edoxaban regimen; HF, heart failure; HR, hazard ratio; ICH, intracranial hemorrhage; LDER, lower-dose edoxaban regimen; NCO, net clinical outcome; NYHA, New York Heart Association; SAPT, single antiplatelet therapy; SEE, systemic embolism event; TIA, transient ischemic attack; VHD, valvular heart disease; VKA, vitamin K antagonist.

Submitted December 29, 2021; accepted December 29, 2021

Reprint requests: Robert P Giugliano, MD, SM, TIMI Study Group, Brigham and Women's Hospital, Hale Building, 7th Floor, Suite 7022, 60 Fenwood Road, Boston, MA 02115
E-mail address: rgiugliano@bwh.harvard.edu.
0002-8703

https://doi.org/10.1016/j.ahj.2021.12.017

Since event rates vary across the range of baseline characteristics, the goal of the analysis was to evaluate the risk-benefit profile in subgroups, particularly among patients at high risk.[4] In addition to considering the effects of individual risk factors, multivariate approaches to identify the combined effects of multiple risk factors may identify subgroup of patients who may benefit the most from novel therapies, particularly when a newer therapy provides a trade off in risk, and benefit.[5,6,7] These predictive approaches based on baseline characteristics aim to detect treatment effect heterogeneity in randomized control trials and integrates risk-modelling approach for translation in medical decision.[8]

Methods

We identified "high-risk" subgroups for inclusion in the analysis, provided the subgroup: (1) Was an established risk factor for adverse events in AF or was of high clinical interest, (2) was previously described in a secondary analysis of the ENGAGE AF-TIMI 48 trial in an original publication in a peer-review journal, 3) had a significantly higher rate of the NCO in the warfarin arm (logrank p-value <0.05) as compared to the corresponding non–high-risk complementary subgroup. Following this definition, some of the previously published subgroups were not included, such as gender, diabetes or liver disease, as they did not meet all criteria.[9-11]

All analyses were conducted in the intention-to-treat population and included first events after randomization, whether on or off study drug. Major bleeding events were analyzed in the safety population (all patients who took at least 1 dose of the study drug).[2,3] Hazard ratios (HR) with 95% confidence intervals (CI) comparing edoxaban with warfarin for each subgroup were calculated using the Cox proportional hazards models with treatment as a covariate, along with stratification factors. The annualized event rates for each of the outcomes in the warfarin vs HDER vs LDER were summarized after dividing the patients into 4 groups: (1) 0 to 1 high-risk factor, (2) 2 high-risk factors, (3) 3 high-risk factors and (4) ≥4 high-risk factors.[7] The HR comparing HDER vs warfarin and LDER vs warfarin were calculated in each strata with an interaction test. Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, Cary, NC) and Stata version 16.1 (College Station, TX).

Results

The 12 subgroups that fulfilled the definition of high-risk (included the following: (1) the elderly (age ≥75 years); (2) increased risk of falls; (3) moderate renal dysfunction (CrCl 30-50 mL/min); (4) prior cerebrovascular disease; (5) concomitant single antiplatelet therapy (SAPT); (6) Vitamin K antagonist (VKA) naïve; (7) history of heart failure (HF); (8) valvular heart disease (VHD); (9) malignancy; (10) prior coronary artery disease (CAD); (11) self-reported as Asian race (AR); and (12) very-low body weight (VLBW, < 55 kg).[12-23] The annualized rates for the primary NCO in the warfarin arm are shown in the Figure 1 and the distribution of each of the subgroup in the 3 arms, including the description of the comparator group in the footnotes, is shown in Table I. The relative efficacy of HDER compared to warfarin for the NCO is shown in Figure 2.

The annualized event rates for the primary efficacy (stroke/SEE) and safety (major bleeding) with warfarin are shown in Supplemental (S) Figures 1 and 2, whereas the relative effects of HDER compared to warfarin on stroke/SEE and major bleeding events are shown respectively in Supplemental Figures 3 and 4.

Elderly patients

In the ENGAGE AF-TIMI 48 trial, 8,474 (40.2%) patients were ≥75 years at randomization.[12] In the warfarin arm (Figure 1), the NCO rate was significantly higher in the elderly (median 79 years, IQR 76, 82) compared to the non–elderly (median 66 years, IQR 60, 70) (11.2% vs 6.2% $P < .001$). In the elderly, HDER significantly reduced the NCO compared to warfarin (HR 0.87, 95%CI 0.79-0.97), and the effect was consistent compared with the non–elderly (HR 0.91, 95%CI 0.82-1.02, P for interaction = 0.55).

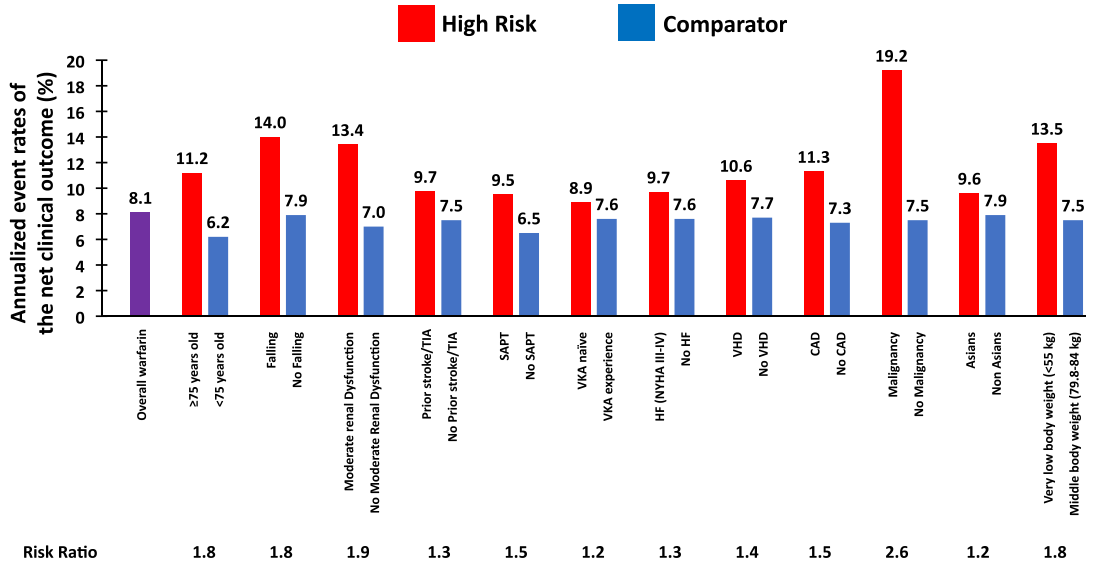
Risk of falling

At randomization, 900 (4.3%) patients were at risk of falling based on 8 prespecified criteria.[13] The NCO rate was significantly higher in patients at risk of falling compared to patients without this risk in the warfarin arm (14.0% vs 7.9% $P < .001$). The HR for the NCO comparing HDER vs warfarin was consistent in patients with (HR 0.96, 95%CI 0.73-1.27) vs without an increased fall risk (HR 0.89, 95%CI 0.82-0.96, P for interaction = 0.60).

Patients with renal dysfunction

Renal dysfunction is a risk factor for both thromboembolic and bleeding complications in patients with AF.[24] At the time of randomization, 4,074 (19.3%) patients had moderate renal dysfunction, and by protocol design[3] these patients received a 50% dose reduction of edoxaban (30 mg reduced from 60 mg for HDER and 15 mg reduced from 30 mg for LDER).[14] In the warfarin arm, the NCO rate was significantly higher in patients with moderate renal dysfunction compared to those with a CrCl >50 mL/min (13.4% vs 7.0% $P < .001$). In these patients with moderate renal dysfunction, HDER significantly reduced the NCO rate compared to warfarin (HR 0.86, 95%CI 0.75-0.98), similar to the effect in those with CrCl >50 mL/min (HR 0.91, 95%CI 0.83-0.99, P for interaction = 0.49).

Figure 1



Annualized event rates (%) of the net clinical outcome in the warfarin arm. The annualized rates of the net outcome (stroke or systemic embolic event, major bleeding, or death) in the warfarin group are shown for all patients randomized to warfarin (purple), high risk subgroups (red), and low risk comparator subgroup (blue). Risk ratios of the NCO (rate in the high-risk subgroup ÷ rate in the low-risk subgroup) are shown below the X-axis. CAD, coronary artery disease; SAPT, single antiplatelet therapy; TIA, transient ischemic attack; VKA, Vitamin K antagonist; VHD, valvular heart disease (Color version of the figure is available online.)

Table I. Baseline characteristics in the warfarin, high-dose edoxaban, and low-dose edoxaban arms of the ENGAGE AF-TIMI 48 trial.

High-risk subgroups*	Warfarin	High-dose edoxaban (60/30 mg dose reduced)	Low-dose edoxaban (30/15 mg dose reduced)
	Number of high-risk/ participants (%)	Number of high-risk/ participants (%)	Number of high-risk/ participants (%)
Elderly (≥75 y old)	2,820/7,036 (40.1)	2,848/7,035 (40.5)	2,806/7,034 (39.9)
Risk of Falling	307/7,036 (4.4)	310/7,035 (4.4)	283/7,034 (4.0)
Moderate Renal Dysfunction† (CrCl ≤50 mL/min)	1,361/7,036 (19.3)	1,379/7,035 (19.6)	1,334/7,034 (19.0)
Prior stroke/transient ischemic attack	1,991/7,036 (28.3)	1,976/7,035 (28.1)	2,006/7,034 (28.5)
Concomitant use of SAPT at 3 mo‡	1,645/6,643 (24.8)	1,642/6,595 (24.9)	1,625/6,671 (24.4)
Vitamin K Antagonist naïve	2,898/7,036 (41.2)	2,895/7,035 (41.2)	2,870/7,033 (40.8)
Heart Failure NYHA III to IV§	904/3,892 (23.2)	897/3,835 (23.4)	834/3,889 (21.4)
Valvular heart disease‖	955/7,023 (13.6)	917/7,008 (13.1)	952/7,015 (13.6)
Coronary artery disease	1,502/7,035 (21.4)	1,478/7,034 (21.0)	1,530/7,033 (21.8)
Malignancy	395/7,036 (5.6)	390/7,035 (5.5)	368/7,034 (5.2)
Asian race	967/7,036 (13.7)	964/7,035 (13.7)	978/7,033 (13.9)
Very-low body weight (<55 kg)¶	368/1,085 (33.9)	344/1,051 (32.7)	370/1,099 (33.7)

CI, confidence intervals; CrCl, creatinine clearance; NYHA, New York Heart Association; SAPT, single antiplatelet therapy.

* All *P*-values comparing the proportion of high-risk patients in the warfarin vs HDER arms were not significant (>.05). The denominators in each subgroup can change according to the choice of the comparator (the control subgroup without the high-risk characteristic).

† Compared with patients with CrCL >50 mL/min.

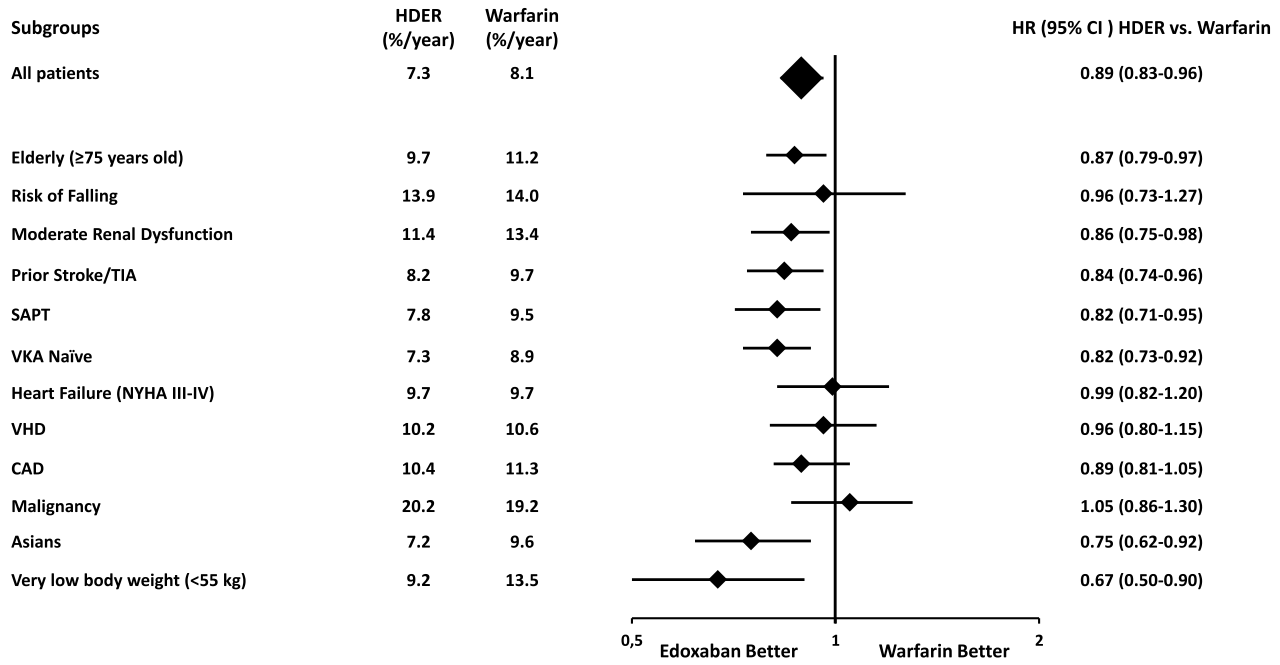
‡ Patients NCO with events occurring before the 3 months visit were excluded. The primary analysis compared SAPT with no SAPT beginning 3 months after randomization.

§ Compared with patients without HF (NYHA stage 0), those with NYHA stage I to II were not included in the analysis.

‖ Patients were considered to have valvular disease if they have at least moderate aortic/mitral regurgitation, aortic stenosis, prior valve repair or valvuloplasty, or prior bioprosthetic replacement of the aortic or mitral valve at baseline.

¶ Compared with patients with middle body weight (79.8-84 kg), those with a body weight between 55 and <79.8 kg, as well as those >84 kg were not included in the analysis.

Figure 2



Net clinical outcome with higher-dose edoxaban regimen vs warfarin in high-risk subgroups. Net clinical outcome: stroke, systemic embolic events, major bleeding, or death from any cause. Abbreviations as in Figure 1 legend.

Previous cerebrovascular events

Patients with previous stroke or transient ischemic attack (TIA) are at increased risk for recurrent ischemic events and bleeding.[25] In the ENGAGE AF-TIMI 48 trial, 5973 (28.3%) patients had prior ischemic stroke or TIA.[15] In the warfarin arm, the risk for the NCO was significantly higher in those with compared to those without previous ischemic stroke or TIA (9.7% vs 7.5% $P < .001$). The relative reduction in the primary NCO with HDER vs warfarin was consistent in patients with (HR 0.84, 95%CI 0.74-0.96) and without previous ischemic stroke or TIA (HR 0.92, 95%CI 0.84-1.00, P for interaction = 0.32).

Treatment with concomitant single antiplatelet therapy (SAPT)

The management of patients with concomitant anticoagulant and antiplatelet agents is challenging since both therapies increase the risk of bleeding.[26] In ENGAGE-TIMI 48, 4912 (24.7%) patients were receiving SAPT at 3 months. In 92% of these the SAPT was aspirin.[16] In the warfarin arm, the risk for the primary NCO was significantly higher in patients with compared to the those without a concomitant SAPT (9.5% vs 6.5%, $P < .001$). In those with SAPT, HDER significantly reduced the primary NCO compared to warfarin (HR 0.82, 95%CI 0.71-0.95), and the effect was consistent compared to those without a concomitant SAPT (HR 0.89, 95%CI 0.81-0.98, P for interaction = 0.35).

Vitamin K antagonist-naïve patients

Patients who have not previously been treated with a VKA are at greater risk for adverse outcomes than VKA-experienced. Using a definition of VKA-naïve as <60 days of continuous VKA use prior to randomization,[17] 8,663 (41.0%) of patients were VKA-naïve prior to randomization.[17] The median time in therapeutic range (INR 2-3) on warfarin for patients who were VKA-naïve were significantly lower than in those who were VKA-experienced (64.6% vs 70.8%, $P < .001$). In the warfarin arm, the primary NCO rate was significantly higher in patients who were VKA-naïve compared vs VKA-experienced (8.9% vs 7.6%, $P = .003$). In VKA-naïve patients, HDER significantly reduced the primary NCO over warfarin (HR 0.82, 95%CI 0.73-0.92); the benefit was even more favorable than in VKA-experienced patients (HR 0.95, 95%CI 0.86-1.05, P for interaction = 0.049).

History of heart failure (HF)

The coexistence of HF and AF worsens clinical outcomes. In the ENGAGE-AF trial, 2635 (12.5%) patients had severe HF (NYHA classes III-IV),[18] and the NCO rate was significantly higher in such patients compared to

those without prior HF (9.7% vs 7.6%, $P = .001$). In patients with HYHA classes III-IV HF, the HR for HDER vs warfarin was 1.00 (0.83-1.21) as compared to 0.87 (0.77-0.98) in patients without HF, with no significant treatment heterogeneity between these subgroups, P for interaction = 0.22).

Valvular heart disease (VHD)

VHD and AF often coexist, and both are independent causes of morbidity and mortality.[27] At baseline, 2824 (13.4%) of patients had a history of significant left-sided VHD, defined as moderate or severe aortic regurgitation, mitral regurgitation, aortic stenosis; aortic or mitral valve repair; or bio-prosthetic aortic or mitral valve replacement.[19] As previously noted, patients with moderate or severe mitral stenosis or a mechanical heart valve were excluded from the trial. In the warfarin arm, the primary NCO rate was significantly higher in patients with vs without VHD (10.6% vs 7.7% $P < .001$). The relative effects of HDER vs warfarin on the NCO were consistent in patients with VHD (HR 0.96, 95%CI 0.80-1.15) compared to those without VHD (HR 0.88, 95%CI 0.81-0.96, P for interaction = 0.41).

Malignancy

Anticoagulation in patients with malignancy is complex because of increased risks of both thrombosis and bleeding, and the frequent need for invasive procedures.[20,28] Patients with active malignancy at randomization were excluded from the ENGAGE AF-TIMI 48 trial; however 1,153 (5.5%) patients were diagnosed with new or recurrent malignancy after randomization, most commonly involving the gastrointestinal tract, prostate, and lung.[20] In the warfarin arm, the primary NCO rate in patients with malignancy was more than twice the rate observed in patients without malignancy (19.2% vs 7.5% $P < .001$). The HRs with HDER vs warfarin were 1.05, 95%CI 0.86 to 1.29 for patients with malignancy, and 0.88, 95%CI 0.81 to 0.95 for patients without malignancy (P for interaction = 0.11).[20] These results were potentially driven by higher risks of gastro-intestinal bleeding with DOAC (higher local concentration of DOAC in the gastro-intestinal mucosa), and potentially increased detection of subsequent gastro-intestinal malignancies.

Coronary artery disease (CAD)

In the ENGAGE AF-TIMI 48 trial, 4510 (21.4%) had established CAD. In the warfarin arm, the NCO rate was higher in patients with compared to patients without established CAD (11.3% vs 7.3% $P < .001$). The relative effect of HDER vs warfarin on the NCO was consistent in patients with (HR 0.91, 95%CI 0.79-1.05) compared to those without CAD (HR 0.89, 95%CI 0.81-0.97, P for interaction = 0.74).

Asian race (AR)

In the ENGAGE AF-TIMI 48 trial, 2,909 (13.8%) of patients were of personally declared AR.[22] They more frequently qualified for a 50% edoxaban dose-reduction due to low body-weight and/or reduced CrCl, thus resulting in lower edoxaban concentration, and anti–FXa activity.[22] In the warfarin arm, the primary NCO rate was significantly higher in Asian patients compared to non–Asians (9.6% vs 7.9% $P = .005$). In AR patients, HDER significantly reduced the primary NCO vs warfarin (HR 0.75, 95%CI 0.62-0.92), while the relative reduction tended to be less in non–AR patients (HR 0.92, 95%CI 0.85-1.00, P for interaction = 0.063).

Very-low body weight (VLBW)

Limited data are available on the efficacy and safety of DOACs in patients at the extremes of weight. The 1,082 (5.1%) patients with VLBW, defined as <55 kg. were compared to 2,153 (10%) patients with middle body weight (MBW; 79.8-84.0 kg), representing the 45th-55th percentiles) in the trial.[23] The pharmacokinetics and pharmacodynamics of HDER were consistent across extremes of body weight for edoxaban concentrations (ng/mL) and endogenous anti–factor Xa activity (IU/mL).[23] The NCO rate was significantly higher in patients with VLBW compared to patients with MBW (13.5% vs 7.5% $P < .001$). In patients with VLBW, HDER (reduced 30 mg dose) significantly reduced the NCO compared to warfarin (HR 0.67, 95%CI 0.50-0.90, $P = .007$); in the MBW patients the HR was 0.89, 95%CI 0.70 to 1.14, P for interaction = 0.14.

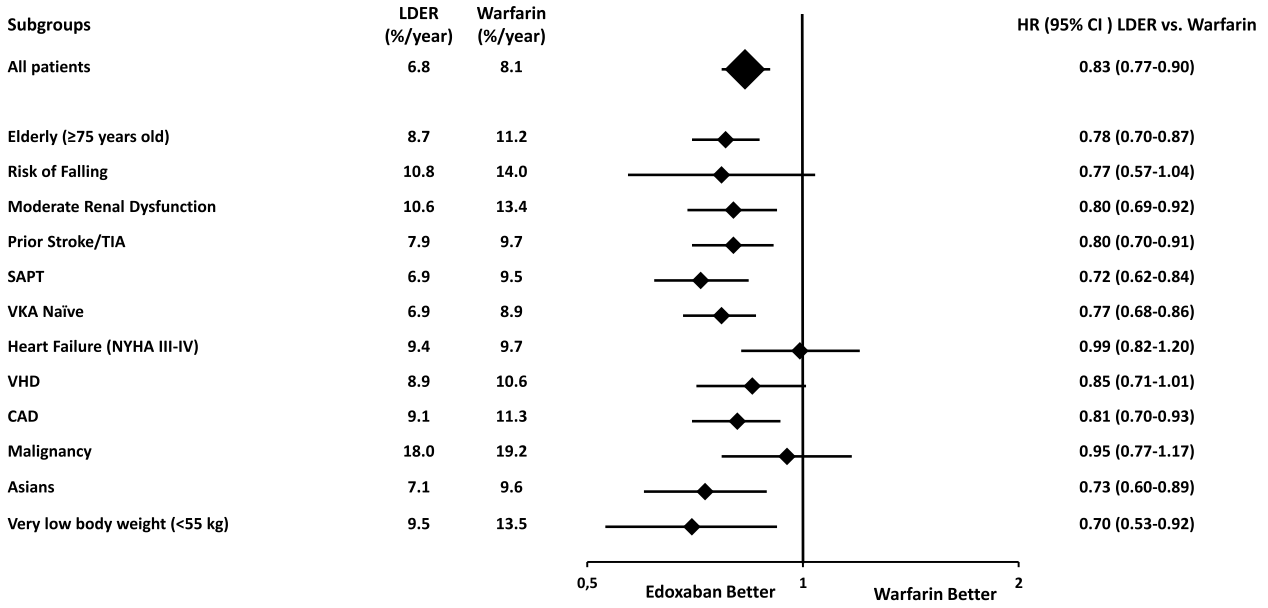
LDER vs Warfarin (Figure 3 and supplemental figures 5-6)

Although LDER (30 mg, dose-reduced to 15 mg) is not approved for clinical use in patients with AF, these results provide insight on the risk-benefit trade-offs when lower intensity anticoagulation is used in patients with AF at high risk of bleeding.[1] These findings are of interest in light of the promising results with edoxaban 15 mg in the ELDERCARE AF trial in Japanese octogenarians who were not candidates for standard dose oral anticoagulants.[29] In ENGAGE AF-TIMI 48, the NCO rates with LDER were numerically lower than with warfarin across all high-risk subgroups, reaching statistical significance for 8 of the 12 high-risk subgroups (Figure 3). The favorable NCOs with LDER were driven by large reductions in major bleeding (Supplemental Figure 6).

Multivariable risk prediction

The risk of the NCO increased with as the number of risk factors increased in the warfarin arm: 4.5%, 7.2%, 9.9% and 14.6% in patients with 0 to 1, 2, 3, and ≥ 4 risk factors, respectively ($P_{trend} < 0.001$) (Figure 4). The treatment effect of HDER vs warfarin was consistent

Figure 3



Net clinical outcome with lower-dose edoxaban regimen vs warfarin in high-risk subgroups. Net clinical outcomes: stroke, systemic embolic events, major bleeding, or death from any cause. Abbreviations as in Figure 1 legend.

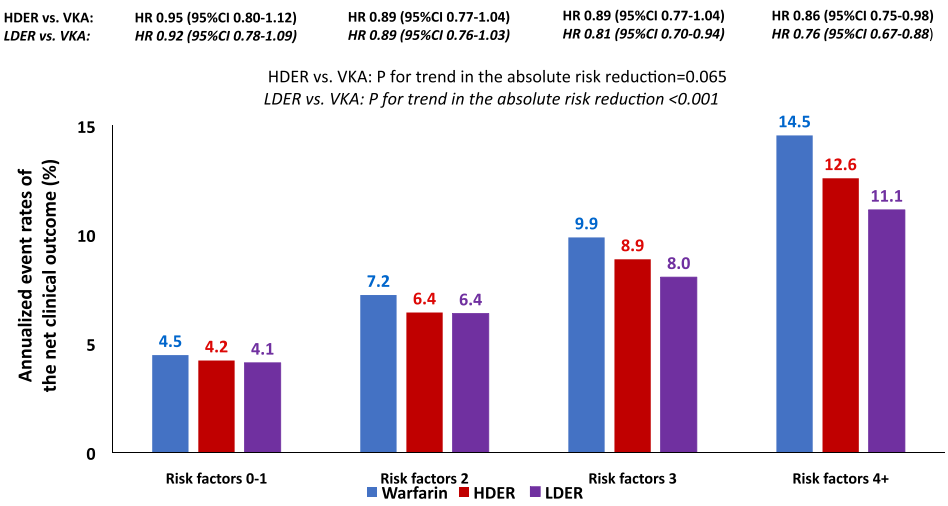
across these 4 categories ($P_{\text{trend for interaction}}$ 0.43), whereas a potential trend was observed with greater benefit of LDER compared with warfarin in higher risk categories ($P_{\text{trend for interaction}}$ 0.061). Since event rates were higher in patients with more risk factors, the absolute risk reduction increased across the 4 categories from 0.3% to 2.0% for HDER vs warfarin and from 0.4% to 3.4% for LDER vs warfarin ($P_{\text{trend for interaction}}$ 0.065, and $P < .001$, respectively). The absolute risk reduction of stroke/SEE with HDER compared with warfarin was greater in patients with a greater number high-risk factors ($P_{\text{trend for interaction}}$ 0.011, Supplemental Figure 7), whereas the difference in the absolute risk of major bleeding was consistent across the 4 categories for HDER vs warfarin ($P_{\text{trend for interaction}}$ 0.24, Supplemental Figure 8) and significantly lowered with LDER compared with warfarin in patients with higher number of risk factors ($P_{\text{trend for interaction}} < 0.001$).

Discussion

In this analysis we observed that across 12 high-risk subgroups of patients with AF after a median follow-up of 2.8 years, the NCO rates in the warfarin arm were the highest in patients with active malignancy (19.2%), those at increased risk of falling (14.0%), and those with very-low body weight (13.5%). When compared to the effects of warfarin, HDER was associated with significant reductions in the primary end point of this analysis (NCO) in 7 of the 12 high risk subgroups driven both with risks of lower stroke/SEE and major bleeding. These included the elderly, patients with moderate renal dysfunction, with prior stroke/TIA, of Asian race, and patients with very-low body weight receiving concomitant SAPT and VKA-naïve patients. The latter was the only subgroup with significant heterogeneity in treatment effect ($P_{\text{int}} = 0.049$). This finding was driven primarily by a more favorable safety profile with edoxaban compared to warfarin that was enhanced in high-risk patients. In 4 of the 12 subgroups (risk of falling, HF, valvular heart disease, coronary artery disease) there was a numeric trend that favored HDER, while in patients with malignancy there was a numeric trend favoring warfarin (Figure 2). The NCO rates with LDER were numerically lower than with warfarin across all high-risk subgroups and driven by lowers rates of major bleeding. We previously observed that the NCO rates were reduced with LDER compared with HDER, also driven by a reduction in major bleeding.[30]

The predictive approaches for treatment effect heterogeneity use a risk-modeling approach where a multivariable model predicts the risk for an outcome and the treatment effect summarized by risk-based subgroups within the trial population.[8] Another approach is to evaluate an effect-modelling by including the interaction term between treatment and baseline subgroups. We have previously shown that both the CHA_2DS_2VASc and TIMI-AF

Figure 4



Annualized event rates (%) of the net clinical outcomes with edoxaban (higher-dose or lower-dose) vs warfarin by the number of risk factors. Net clinical outcomes: stroke, systemic embolic events, major bleeding, or death from any cause. Abbreviations as in Figure 1 legend.

risk scores predicted higher rates of stroke/SEE, major bleeding,[31] and of the NCO in the warfarin arm of the ENGAGE AF-TIMI 48 population.[32] The current findings support the relevance of using a multivariable risk prediction model to evaluate the benefits and the harms of a therapy and to confirm the most appropriate treatment choices.[7]

Edoxaban has been widely studied in a variety of patients with AF and in other cardiovascular conditions.[33-41] In addition, extensive supportive pharmacokinetic and pharmacodynamic (including both endogenous and exogenous FXa inhibition) data support the clinical efficacy and safety data.[42-44] Lastly, an ongoing large international registry (Edoxaban Treatment in routine clinical practice for patient with non–valvular AtriaL Fibrillation, ETNA-AF) in over 25,000 patients has provided additional information on the efficacy and safety of edoxaban in clinical practice, [45,46] Additional data with this agent (as well as other DOACs) in patients at extremes of body weight and renal function, and at high risk of bleeding are needed.

Perspectives

Since underuse of anticoagulation in high-risk patients with AF remains common, substitution of effective and safer alternatives to warfarin, such as edoxaban, represents a major opportunity to improve clinical outcomes.

Limitations

We acknowledge several limitations of this analysis. Some high-risk conditions, such as severe renal dysfunction (CrCl of $\leq$30 mL/min) or patients treated with dual antiplatelet therapies were excluded from the trial. The ENGAGE AF-TIMI 48 trial was not powered to identify treatment effect in specific subgroups or to detect heterogeneity of outcomes between subgroups. However, the trial was large enough (nearly 60,000 patient years of observation) to support the general conclusions. Finally, we analyzed all pre-specified subgroups as well as other post hoc subgroups from the literature. Unlike analyses of single subgroups, we analyzed a broad range of high-risk subgroups using an objective criterion (a significantly higher rate of the net clinical outcome than the complementary subgroup) of an outcome that combined the key efficacy, and safety end point, as well as all-cause death.

Conclusion

Analyses of 12 high-risk subgroups of patients in the ENGAGE AF-TIMI 48 trial support favorable net clinical outcomes with HDER and LDER compared with warfarin across a broad range of vulnerable patients. As it is impractical to conduct large randomized clinical trials with adequate power for each of these high-risk subgroups, this secondary analysis from the largest such trial helps to inform clinical decision-making in these challenging patients.

Author contributions

Dr Giugliano had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures

Dr Gencer's research activities in the TIMI Group are supported by grants from Geneva University Hospitals, Eugenio Litta, and Arthemis Foundations. Dr Antman has received grant support through his institution from Daiichi-Sankyo. Dr Ruff reports receiving research grants through his institution: Anthos Therapeutics, Boehringer Ingelheim, Daiichi Sankyo, MedImmune, National Institutes of Health. Honoraria for scientific advisory boards and consulting: Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Janssen, MedImmune, Pfizer, Portola. Dr Braunwald reports a research grant to his institution from Daiichi-Sankyo. Outside the submitted work, Dr Braunwald reports research grants through his institution from AstraZeneca, Daiichi Sankyo, Merck, and Novartis; and consultancy fees from Amgen, Boehringer-Ingelheim/Lilly, Cardurion, Myokardia, NovoNordisk, and Verve. Ms Murphy reports receiving grants from Abbott Laboratories, Amarin, Amgen, AstraZeneca, Critical Diagnostics, Daiichi Sankyo, Eisai, GlaxoSmithKline, Intarcia Therapeutics, Merck and Co, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, Medimmune, Janssen Research Development, and Genzyme and personal fees from Amgen. Dr Giugliano reports clinical trials/research support to his institution from: Daiichi-Sankyo, Anthos Therapeutics, and Amgen. Dr, Giugliano also reports honoraria for CME lectures and/or consulting from Amarin, the American College of Cardiology, Amgen, Astra Zeneca, CryoLife, CVS Caremark, Daiichi Sankyo, Dr Reddy's Laboratories, Esperion, Gilead, GlaxoSmithKline, Hengrui, Inari, Menarini, Merck, PhaseBio Pharmaceuticals, Pfizer, SAJA Pharmaceuticals, St Lukes Hospital (Kansas City), Samsung, and Servier.

Funding

The ENGAGE AF-TIMI 48 study was supported by Daiichi Sankyo Pharma Development.

Role of the funder/sponsor

Daiichi Sankyo was involved in designing and collecting data for the ENGAGE AF-TIMI 48 trial, and the named co-authors from Daiichi Sankyo participated in the data interpretation and drafting of this report, but had no role in data analysis. The TIMI Study Group had access to all the data, conducted all analyses, and had final responsibility for the decision to submit the article for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.12.017.

References

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS). Eur Heart J 2021;42:373–498.
2. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.
3. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor XA next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010;160:635–41.
4. Lip GYH. The safety of NOACs in atrial fibrillation patient subgroups: a narrative review. Int J Clin Pract 2019;73:e13285.
5. Ferreira JP, Gregson J, Duarte K, et al. Individualizing treatment choices in the systolic blood pressure intervention trial. J Hypertens 2018;36:428–35.
6. Pocock SJ, Stone GW, Mehran R, Clayton TC. Individualizing treatment choices using quantitative methods. Am Heart J 2014;168:607–10.
7. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6:18.
8. Kent DM, Paulus JK, van Klaveren D, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement. Ann Intern Med. 2020;172:35–45.
9. Zelniker TA, Ardissino M, Andreotti F, et al. Comparison of the efficacy and safety outcomes of Edoxaban in 8040 women versus 13 065 men with atrial fibrillation in the ENGAGE AF-TIMI 48 Trial. Circulation 2021;143:673–84.
10. Plitt A, Ruff CT, Goudev A, et al. Efficacy and safety of edoxaban in patients with diabetes mellitus in the ENGAGE AF-TIMI 48 trial. Int J Cardiol 2020;304:185–91.
11. Qamar A, Antman EM, Ruff CT, et al. Edoxaban versus warfarin in patients with atrial fibrillation and history of liver disease. J Am Coll Cardiol 2019;74:179–89.
12. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of Edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc 2016;5(5).
13. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 analysis. J Am Coll Cardiol 2016;68:1169–78.
14. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with Edoxaban in the ENGAGE AF-TIMI 48 trial. Circulation 2016;134:24–36.
15. Rost NS, Giugliano RP, Ruff CT, et al. Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from ENGAGE AF-TIMI 48 (effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48). Stroke 2016;47:2075–82.
16. Xu H, Ruff CT, Giugliano RP, et al. Concomitant use of single antiplatelet therapy with edoxaban or warfarin in patients with atrial fibrillation: analysis From the ENGAGE AF-TIMI48 trial. J Am Heart Assoc 2016;5(2).
17. O'Donoghue ML, Ruff CT, Giugliano RP, et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillationdagger. Eur Heart J 2015;36:1470–7.
18. Magnani G, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban compared with warfarin in patients with atrial

fibrillation and heart failure: insights from ENGAGE AF-TIMI 48. Eur J Heart Fail 2016;18:1153–61.
19. De Caterina R, Renda G, Carnicelli AP, et al. Valvular heart disease patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol 2017;69:1372–82.
20. Fanola CL, Ruff CT, Murphy SA, et al. Efficacy and safety of Edoxaban in patients with active malignancy and atrial fibrillation: analysis of the ENGAGE AF - TIMI 48 trial. J Am Heart Assoc 2018;7: e008987. doi:10.1161/JAHA.118.008987.
21. Zelniker TA, Ruff CT, Wiviott SD, et al. Edoxaban in atrial fibrillation patients with established coronary artery disease: insights from ENGAGE AF-TIMI 48. Eur Heart J Acute Cardiovasc Care 2019;8(2):176–85.
22. Chao TF, Chen SA, Ruff CT, et al. Clinical outcomes, Edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. Eur Heart J 2019;40:1518–27.
23. Boriani G, Ruff CT, Kuder JF, et al. Edoxaban versus Warfarin in patients with atrial fibrillation at the extremes of body weight: an analysis from the ENGAGE AF-TIMI 48 Trial. Thromb Haemost 2021;121:140–9.
24. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) and ATRIA (AnTicoagulation and risk factors in atrial fibrillation) study cohorts. Circulation 2013;127:224–32.
25. Kirchhof P, Benussi S, Kotecha D, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.
26. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019;381:1103–13.
27. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. Eur Heart J 2014;35:3328–35.
28. Mosarla RC, Vaduganathan M, Qamar A, et al. Anticoagulation strategies in patients with cancer: JACC review topic of the week. J Am Coll Cardiol 2019;73:1336–49.
29. Okumura K, Akao M, Yoshida T, et al. Low-dose Edoxaban in very elderly patients with atrial fibrillation. N Engl J Med 2020;383:1735–45.
30. Steffel J, Ruff CT, Yin O, et al. Double-blind comparison of half-dose versus full-dose Edoxaban in 14,014 patients with atrial fibrillation. J Am Coll Cardiol 2021;77:1197–207.
31. de Groot JR, Ruff CT, Murphy SA, et al. Edoxaban versus warfarin in patients with atrial fibrillation in relation to the risk of stroke: a secondary analysis of the ENGAGE AF-TIMI 48 study. Am Heart J 2021;235:132–9.
32. Fanola CL, Giugliano RP, Ruff CT, et al. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. Eur Heart J 2017;38:888–96.
33. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615–24.
34. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394:1335–43.
35. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet 2016;388:1995–2003.
36. Moll F, Baumgartner I, Jaff M, et al. Edoxaban plus Aspirin vs dual antiplatelet therapy in endovascular treatment of patients with peripheral artery disease: results of the ePAD trial. J Endovasc Ther 2018;25:158–68.
37. Van Mieghem NM, Unverdorben M, Valgimigli M, et al. Edoxaban versus standard of care and their effects on clinical outcomes in patients having undergone transcatheter aortic valve implantation in atrial fibrillation-rationale and design of the ENVISAGE-TAVI AF trial. Am Heart J 2018;205:63–9.
38. Colonna P, von Heymann C, Santamaria A, et al. Routine clinical practice in the periprocedural management of edoxaban therapy is associated with low risk of bleeding and thromboembolic complications: The prospective, observational, and multinational EMIT-AF/VTE study. Clin Cardiol 2020;43:769–80.
39. Hohnloser SH, Camm J, Cappato R, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. Eur Heart J 2019;40:3013–21.
40. Inoue H, Yamashita T, Akao M, et al. Prospective observational study in elderly patients with non-valvular atrial fibrillation: rationale and design of the All Nippon AF In the elderly (ANAFIE) registry. J Cardiol 2018;72:300–6.
41. Ohashi Y, Ikeda M, Kunitoh H, et al. Venous thromboembolism in patients with cancer: design and rationale of a multicentre, prospective registry (Cancer-VTE Registry). BMJ Open 2018;8: e018910. doi:10.1136/bmjopen-2017-018910.
42. Salazar DE, Mendell J, Kastrissios H, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. Thromb Haemost 2012;107:925–36.
43. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015;385:2288–95.
44. Yin OQP, Antman EM, Braunwald E, et al. Linking endogenous factor Xa Activity, a biologically relevant pharmacodynamic marker, to edoxaban plasma concentrations and clinical outcomes in the ENGAGE AF-TIMI 48 trial. Circulation 2018;138:1963–73.
45. de Groot JR, Weiss TW, Kelly P, et al. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. Eur Heart J Cardiovasc Pharmacother 2021;7:f30–9.
46. De Caterina R, Agnelli G, Laeis P, et al. The global Edoxaban treatment in routine clinical practice (ETNA) noninterventional study program: rationale and design. Clin Cardiol 2019;42:1147–54.