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Impact of edoxaban-related adverse events in patients with cancer experiencing venous thromboembolism during antineoplastic therapy: Results of the phase IV EDOI study (GOIRC-05–2018)☆

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ABSTRACT

Background: The oral factor Xa inhibitor, edoxaban, is effective and safe in cancer-associated Venous Thromboembolism (VTE) treatment. The EDOI study aims to evaluate compliance and quality of life (QoL) in patients with cancer-associated VTE treated with edoxaban during antineoplastic care.

Material and methods: The EDOI was a multicentre phase IV, single-arm study. Patients received edoxaban for at least 6 months. The primary objective was to evaluate the rate and 90 % Confidence Intervals of edoxaban-related adverse events (AEs) with impact on antineoplastic therapy in terms of delays, reduction, or interruption. Mixed models for repeated measure have been adopted to evaluate the secondary endpoint as the change of QoL scores from enrolment to 6 months.

Results: From July 2019 to March 2021, 147 patients were enrolled. Edoxaban-related AEs with impact on antineoplastic therapy were observed in 7 patients (4.76 %; 90 %CI 2.23 %-8.94 %). The cumulative incidence of AEs was 2.7 % at 1 month from enrolment. A statistically significant increase ($p < 0.05$) was observed for mean changes in PACT-Q2 Convenience (+5 points) and Satisfaction (at least +2.5), and reduction of ACTS Burden (at least +1.7) at 1 month. Overall QoL measured by FACT-G shows a mean increase in the first month (+1.3), while decreases in the subsequent 5 months (-2.5).

Conclusion: The results of the EDOI Study demonstrate that edoxaban was well tolerated in patients receiving cancer treatment, showing a low rate of AEs with an impact on antineoplastic therapy, mainly within the first 30 days of administration. Lastly, the edoxaban-related AEs did not result in a lower overall QoL.

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1. Introduction

Venous thromboembolism (VTE) is a common and clinically important disease that could occur in patients with cancer [1]. Treatment of cancer-associated VTE is challenging, and the risks of recurrent thrombosis and bleeding are higher among cancer patients [2]. These events could contribute to mortality and morbidity and may interfere with cancer treatment with an increased risk of hospitalization.

Anticoagulant therapy with low-molecular-weight heparin (LMWH), given for both initial and long-term treatment, has been the preferred approach recommended by practice guidelines [3,4]. Recently, direct oral anticoagulants (DOACs) have been introduced in clinical practice. The NCCN Guidelines indicate that DOACs are effective for VTE treatment with lower occurrence and severe bleeding [5]. Moreover, cancer-associated VTE patients should be treated with anticoagulation for a minimum of 6 months.

Several phase III randomized trials confirmed the efficacy and safety of DOACs in cancer-associated VTE patients [6–10].

In the SELECT-D trial [6], showed lower recurrent VTE in the rivaroxaban arm, without a significant increase in major bleeding (6 % vs 4 %; HR: 1.83; 95 % CI: 0.68–4.96) compared to deltaparin.

Similarly, the ADAM-VTE trial [7] exhibited of apixaban in terms of major bleeding (0 % vs 1.4 %, $p = 0.138$) vs dalteparin arm. Moreover, the CARAVAGGIO trial [8] confirmed the non-inferiority of apixaban vs dalteparin (3.8 % and 4.0 %, respectively).

Finally, in a phase III, non-inferiority HOKUSAI-VTE Cancer trial, randomized to receive either LMWH for at least 5 days followed by oral edoxaban or dalteparin [9]. The recurrent VTE rate was lower in edoxaban arm (7.9 % and 11.3 %), while the rate of major bleeding was significantly higher with edoxaban than with dalteparin (6.9 % and 4.0 %) mainly due to the higher rate of upper gastrointestinal bleeding occurring in gastrointestinal cancer patients.

Although these data are encouraging, modest evidence exists on the use of DOACs in cancer-associated VTE patients in the real world as well as on 12-month follow-ups [10–12].

More research is needed to understand how patients respond to DOACs and how they may influence the management of cancer patients as treatments and side effects.

We designed the phase IV EDOI study to evaluate the impact of edoxaban-related AEs on antineoplastic therapy and the change in the quality of life (QoL) of patients with cancer-associated VTE.

2. Material and methods

2.1. Study design and participants

The EDOI (EUDRACT 2018–003833–14) was a multicenter, phase IV, single-arm study to evaluate the real-life clinical management of Edoxaban treatment in patients with cancer-associated VTE.

Cancer-associated VTE patients during antineoplastic treatment candidates to receive anticoagulant therapy were enrolled. Patients had to be receiving systemic antineoplastic therapy (such as chemotherapy, target therapy, immunotherapy, and hormonal therapy), for further at least 3 months.

Vascular abnormalities or current or recent major bleeding were considered exclusion criteria.

Approval for the study was obtained from the AVEN ethics committee of Modena (Italy) and further details are summarized in Supplementary materials.

2.2. Interventions and study procedures

Patients enrolled received edoxaban as per clinical practice.

Clinical visits and endpoint assessments were performed at baseline, after 1 month, 3 months, and 6 months, while instrumental exam and local laboratory test were performed if clinically indicated. Further details regarding edoxaban dosage and duration and clinical procedures are specified in Supplementary materials.

2.3. Study endpoints

The primary endpoint was the number of patients with at least one antineoplastic therapy delay, reduction, or interruption due to Adverse Drug Reaction (ADR) (bleeding, hepatobiliary toxicity, renal toxicity, anemia, hypersensitivity reactions) related to edoxaban. The secondary endpoint reported in this article was the modification over time (at baseline, 1 month, 3 months and 6 months) in patient-reported outcomes (PROs) during edoxaban treatment measured by Functional Assessment of Cancer Therapy – General (Fact-G), Perception of Anti-Coagulant Treatment Questionnaire 2 (PACT-Q2), and Anti-Clot Treatment Scale (ACTS) questionnaires. The remanent secondary endpoints regarding the compliance to edoxaban treatment and description of safety events will be reported in a separate and subsequent article.

2.4. Statistical analysis

The sample size was defined to estimate the levels of precision of Confidence Intervals (CIs) around the unknown primary endpoint rate.

Hence, was performed a simulation basing on a range of expected rate from 10 % to 15 %. Given a sample size of 150 patients the width of the 90 % CIs (under the Poisson distribution assumption) will be equal 0.085 and 0.11 respectively. The result for the primary endpoint is presented by the rate of patients with edoxaban-related AEs with impact on antineoplastic therapy and its corresponding Poisson 90 % CIs. A post-hoc test for a single proportion will allow testing if the AEs rate is lower than 10 % (within the threshold identified as a common or less frequent event rate, according to EMA). The first primary endpoint was also analyzed for its dependence on time, thus cumulative incidence of AEs was graphically depicted using Aalen-Johansen curves, and the significance of the differences between hazard sub-distributions was tested using the Fine-Gray model. A ring plot was performed to illustrate AEs distribution by tumor site. Patient Reported Outcomes (PROs) were analyzed according to their specific scoring guideline. Global and subscale scores were shown by descriptive statistics per each study time point (baseline, 1 month, 3 months, 6 months). Multivariable Linear Mixed-Effects Models for Repeated Measure (MMRM) were implemented to analyze changes in PROs among follow-up.

All the statistical analyses were made using R Statistical software, version 4.3.

3. Results

3.1. Patient characteristics

Between July 8, 2019, and March 31, 2021, 150 cancer patients with VTE candidates to receive complete anticoagulant treatment were screened in 21 sites in Italy. Among all, 147 patients were eligible and evaluable (Fig 1).

Baseline characteristics are listed in Table 1. Almost all patients were Caucasian (99.3 %), equally represented per sex (71 females, 48.3 %), and with a ECOG PS 0–1 (80, 56.7 %, and 54, 38.3 % respectively). The median age was 69 (range 32–86) years, median weight of 70 (40−110) kilograms. The most common primary tumor site was the lung with 39 (26.5 %) followed by 26 colorectal (17.7 %) and 18 pancreatic (12.2 %) tumors; almost all patients were in stage IV (81 %) and received chemotherapy (83.7 %) as antineoplastic agent. Immunotherapy and target therapies were administered in 21.8 % and 18.4 % of patients, respectively. Lastly 52.4 % of patients had venous thrombosis, while the remaining had pulmonary embolism.

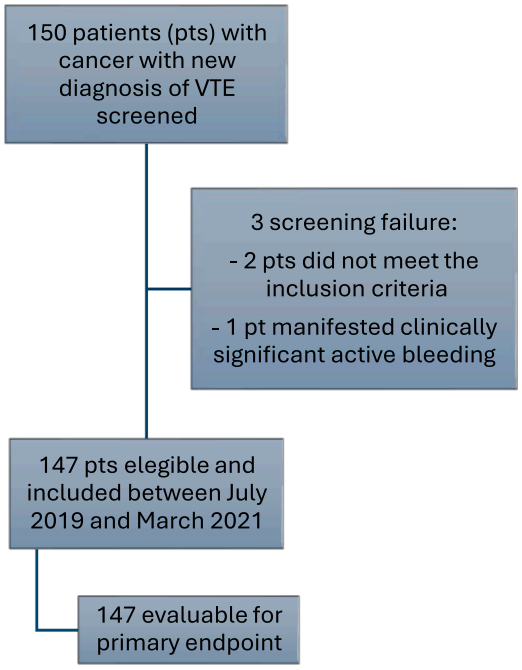

Fig. 1. Flow diagram of the EDOI Study.

3.2. Edoxaban-related AEs with impact on antineoplastic therapy

Among 147 evaluable patients, none performed a reduction of antineoplastic therapy due to ADR to edoxaban, in four (2.7 %) a delay occurred, and in three (2.0 %) the interruption of the antineoplastic therapy was recorded. Accordingly, the primary endpoint rate was 4.76 % (7 out of 147) with 90 % confidence interval ranging from 2.23 % to 8.94 %. Thus, by a post-hoc test, the primary endpoint occurrence rate $\geq$ 10 % hypothesis was rejected with a p-value of 0.024. The cumulative incidence rate of the AEs at 6 months follow-up was depicted in Fig 2.

At least one AE (blue line) was recorded in 45 out of 147 (30.6 %) patients. Of these, 27 (60 %) were related to edoxaban with a cumulative incidence rate at 1 month equal to 9.5 % (orange line). Otherwise, among the 7 patients in which the primary outcome occurred, the cumulative incidence rate at 1 month was 2.7 % (red line).

Thus, 14 out of 27 (51.9 %) edoxaban-related AEs occurred in the first month and since the cumulative incidence was reduced by 1 % per each day of subsequent edoxaban intake (HR:0.990, 95 %CI 0.985–0.995, $p < 0.001$).

Lastly, the distribution of AEs was also assessed by the primary tumor site. As depicted in Fig 3, a higher incidence of AEs was observed in patients with gastrointestinal tumors (22 out of 68, 32.4 %) with a limited impact on AT. The same percentage of edoxaban-related AEs with impact on antineoplastic therapy was observed in gastrointestinal and breast cancer patients (7.35 and 7.14 %, respectively).

3.3. Quality of life – Fact-G questionnaire

The QoL outcomes measured by Fact-G and its sub-scale scores were summarized in Table S1 and depicted in Figure S1.

The percentage of non-responders to the Fact-G questionnaire increased from 9.5 % to 60.5 % from the baseline to 6 months (Table S1). The increase in the non-responders monthly rate was also related to the deaths occurred within 6 months (42 out of 68 of all deaths occurred during the entire study, Table S2).

At 1 month the mean score was stable to a value of 69, gaining + 3 points from the baseline mean score (Table S1). The results from the univariable model show no significant difference in score change over time. However, by the post-hoc comparison, a reduction of Fact-G score from 1 month to 3 months was found, without reaching statistical significance (-1.74, p-value 0.071; Table S3). The magnitude of the decrease was also higher considering the difference from 6 months to 1 month (i.e., −1.74–0.73 =-2.47 points).

Table 1
Baseline characteristics.

Characteristics	N = 147
Age	
Median (years)	69
Range	(32–86)
Interquartile range	(61, 75)
Gender, n(%)	
Female	71 (48.3)
Male	76 (51.7)
Ethnicity, n(%)	
Caucasian	146 (99.3)
African	1 (0.7)
Weight	
Median (years)	70
Range	(40–110)
Interquartile range	(60, 79)
ECOG PS status, n(%)	
0	80 (56.7)
1	54 (38.3)
2	7 (5.0)
Unknown	6
Smoking habit, n(%)	
Never	61 (50.8)
Former	38 (31.7)
Current	21 (17.5)
Unknown	27
Tumor site, n(%)	
Upper/lower gastrointestinal	68 (46.3)
Colorectal	26 (17.7)
Pancreas	18 (12.2)
Stomach	12 (8.2)
Liver	2 (1.4)
Others	10 (6.8)
Lung	39 (26.5)
Genitourinary/Gynecological	16 (10.9)
Urinary tract	4 (2.7)
Kidney	3 (2.0)
Prostate	2 (1.4)
Ovarian	4 (2.7)
Uterus	3 (2.0)
Breast	14 (9.5)
Others	9 (6.1)
Tumor stage, n(%)	
I	4 (2.7)
II	4 (2.7)
III	20 (13.6)
IV	119 (81)
Antineoplastic therapy, n(%)	
Chemotherapy	123 (83.7)
Immunotherapy	32 (21.8)
Targeted therapy	27 (18.4)
Hormonal therapy	2 (1.4)
Tumor treatment setting, n(%)	
Neoadjuvant	3 (2.0)
Adjuvant	10 (6.8)
1 line	84 (57.1)
2 line	37 (25.2)
3 line	6 (4.1)
> 4 lines	6 (4.1)
Concomitant CRT	1 (0.7)
Type of VTE, n(%)	
Pulmonary embolism	70 (47.62)
Venous Thrombosis	77 (52.38)
Comorbidities, n(%)	
Hypertension	
No	76 (51.7)
Yes	71 (48.3)
Diabetes	
No	119 (80.9)
Yes	28 (19.1)

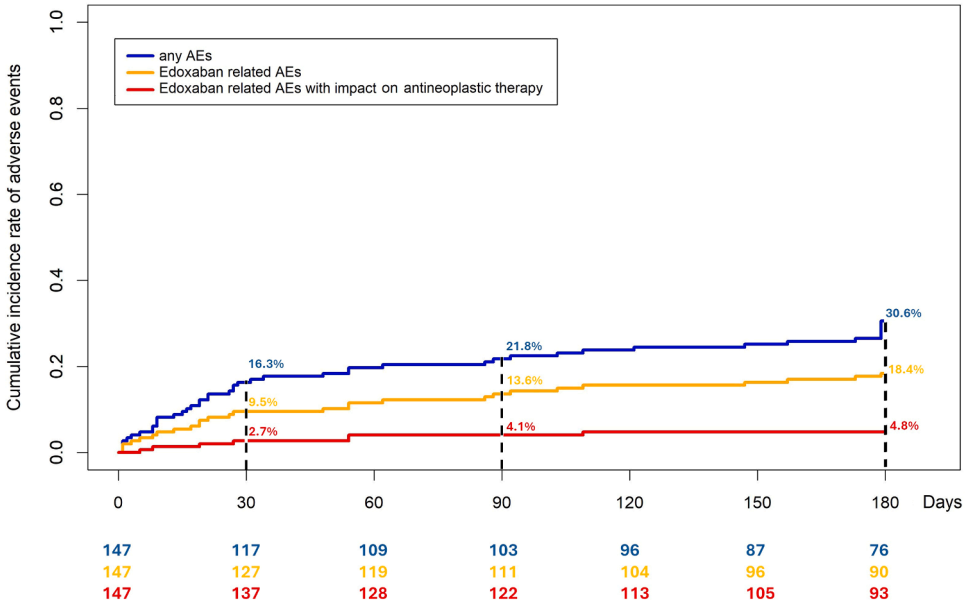

Fig. 2. Cumulative incidence rate of adverse events via Aalen Johansen curve.

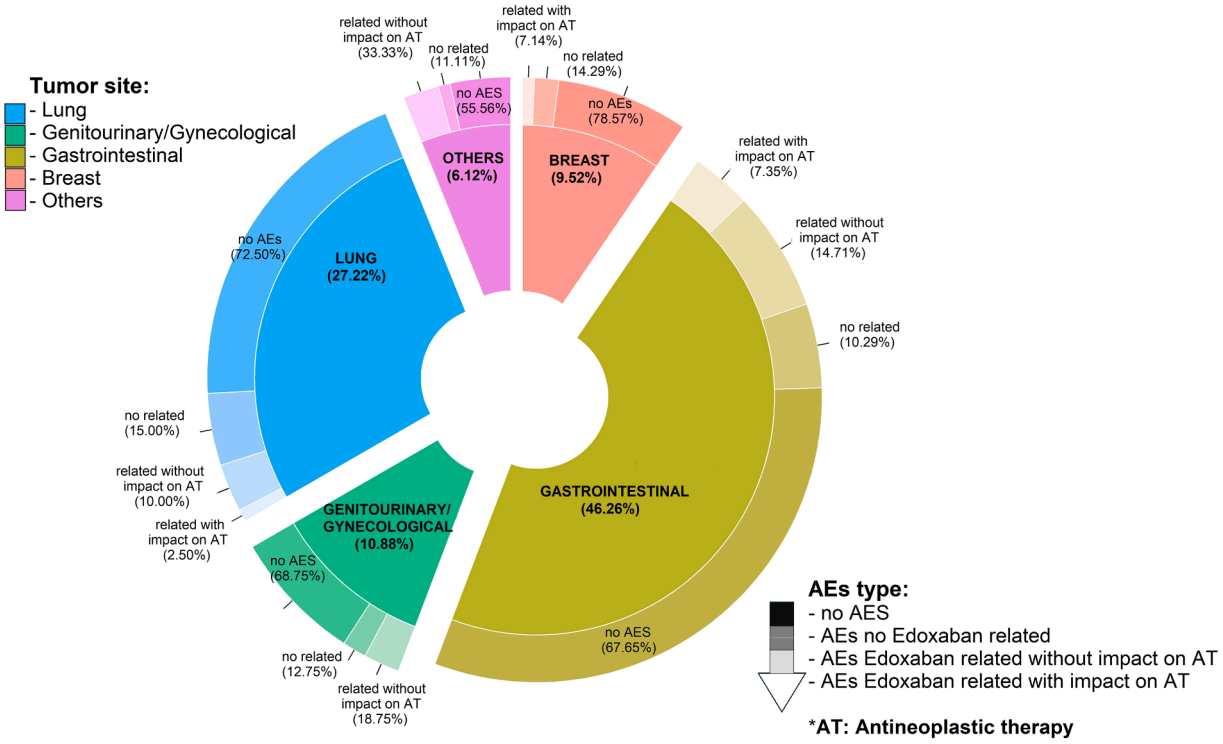

Fig. 3. Donut plot: AEs type per primary tumor site. The most internal circle shows EDOI patients divided per tumor-site. Per each site, depicted in different colors, relative frequencies were reported. Instead, the external circle represents the division per AEs type occurred during the follow-up. Relative frequencies of AEs type are reported and calculated per each tumor site. The darker tonality indicated "no AEs" occurred, while the lighter represent: i) "AEs no Edoxaban related"; ii) "AEs related to Edoxaban but without impact on antineoplastic therapy"; iii) "AES related to Edoxaban with impact on antineoplastic therapy " (primary endpoint).

Adding the first event type occurred within the 6-month variable (Table S2) in the MMRM model, different intercepts per type event (Figure S2), and slightly diverse trend per level of patients measured by the mean of the st.dev within component $\tau_{11 \text{ id. time}}$ 2.8 on the residual 5.99 were observed (Table S4).

The multivariable analysis shows diabetes and death during the study period as factors associated with a lower QoL score (-6.9, 95 %CI −12.4–1.4, p = 0.015 and −6.7, 95 %CI −11.1–2.3, p = 0.003; respectively), and male sex and edoxaban-related AEs within 6 months as factors associated with a higher QoL score (+4.0, 95 %CI −0.4–8.3, p = 0.07 and +5.9, 95 %CI 0.1–11.7, p = 0.045) (Table 2).

3.4. Perception of anti-coagulant treatment - PACT-Q2 questionnaire

The patient-reported outcomes using the PACT-Q2 sub-scale Convenience and Satisfaction score were summarized in supplementary

Table S5.

A significant increase of at least 5 points was observed during the entire follow-up compared to the baseline in the mean Convenience score. The multivariable analysis does not show any relevant difference per any factors. Also for the Satisfaction score, was observed an increasing trend during the time (at least +2.57 mean point) and achieved the maximum average at 3 months from the baseline (+5.1, 95 % CI 2.22–7.99, p = 0.001). Patients who received edoxaban for at least 6 months had a higher mean score (B=9.68, 95 %CI 3.38–15.97, p = 0.003) (Table 2).

3.5. Anti-clot treatment scale – ACTS questionnaire

The patient-reported outcomes using the ACTS sub-scale Burdens and Benefits score were summarized in Table S5. A significant increase of at least 1.7 points was observed during the entire follow-up compared to the baseline in the mean Burden score. Instead, any relevant change during the follow-up period was observed for the Benefits sub-scale score but patients with a gastric primary tumor site showed significantly higher Benefit scores compared to the other patients (+ 1.03 points, 95 %CI: 0.30 – 1.76; p = 0.006) (Table 2).

3.6. Association among the perception and satisfaction of anti-coagulant treatment and quality of life

Among the subscales of PACT-Q2 and ACTS questionnaires, the most significant association with Fact-G score was found with the Satisfaction and Burden subscales. Per each increase of 1 point of the two subscales (PACT-Q2 Satisfaction and ACTS Burdens), the Fact-G scores increased by + 0.35 (p = 0.001) and + 0.67 points (p = 0.001), respectively.

4. Discussion

The EDOI study is the first phase IV trial designed to understand the management of the AEs related to edoxaban treatment in VTE-associated heterogeneous cancer populations.

This trial showed that any grade incidence rate of edoxaban-related AEs was 18.4 %, slightly lower than the 22.6 % observed in the HOKUSAI-VTE Cancer Trial [9].

Most relevant, according to the primary objective, the EDOI trial determined the incidence rate of edoxaban-related AEs with impact on antineoplastic therapy was about 5 % and, although through a post-hoc analysis, sustain that the hypothesis of a “very common” event, corresponding to an average rate ≥ 10 % according to European Medicines Agency (EMA) definitions, could be rejected (p = 0.024). However, 3 out 7 of edoxaban-related AEs required a definitive interruption of the antineoplastic therapy which is the worst scenario considered in our study (AT delays or reduction or interruption). Furthermore, the interruption could be also considered as a detrimental prognostic event since all of these 3 patients died within a maximum of 50 days after edoxaban discontinuation.

Additionally, we found that > 50 % of the overall AEs and edoxaban-related AEs with or without impact on antineoplastic therapy occurred during the first month of enrolment. This result appears particularly earlier compared to data from other phase III trials with DOACs [8,9]. Our study shows the same rate of patients who received edoxaban treatment for at least 6 months as the HOKUSAI-VTE Cancer trial (57.1 % and 58.1 %). However, observing the event-free survival curves from CARAVAGGIO and HOKUSAI-VTE Cancer trials [8,9], it seems that 50 % of the events were captured not earlier than the first two and four months from the enrolment, respectively. Clinicians should be more conservative, taking into account our results, that the occurrence rate of AEs is not progressively spread over time, but more observed within the first month of treatment.

Finally, regarding the different management of DOACs per tumor site, the EDOI trial confirmed that patients with primary gastrointestinal tumors exhibited a higher number of any AEs. However, despite the limitation of a heterogeneous and small sample size, the same percentage (~ 7 %) of edoxaban-related AEs with consequent impact on antineoplastic therapy was also observed in patients with breast cancer.

Another relevant topic handled in the EDOI study as a secondary objective was the change of QoL within 6 months from the enrolment. Regarding the overall QoL, despite a score gain observed from descriptive analysis (+3 mean points), the results of MMRM models allowed us to observe that the increase was limited in the first month after the start of treatment (+1.3), while the score decreases in the subsequent 5 months (-2.5). This trend could be driven by several factors. However, this seems to capture the initial benefit of the anticoagulant treatment but, in the following months, several concomitant and related patient factors such as further line of antineoplastic agents, disease progression, and tumor burden, could justify the subsequent worsening.

In contrast to the overall decrease, the multivariable analysis shows that the 27 patients who had AEs related to edoxaban had a higher average QoL. This result should not be interpreted to sustain a better QoL of this subgroup, indeed it simply suggests the lack of association with the worsening of QoL.

Regarding the other two questionnaires, PACT-Q2 and ACTS respectively, increasing trends in scores were observed over time, except for the perception of the benefit of anticoagulant therapy, which seemed steady over time but appeared “more appreciated” by patients with gastric cancer.

Comparing the CANVAS trial [13] to our study, the mean of the ACTS benefit and burden scores were similar but slightly higher (+1 and +2, respectively). This difference could depict a more frail population in our study since the 6-month death rate was 46.3 % vs 21.5 %, respectively. In patients who have higher expectations for satisfaction (PACT-Q2) and burden reduction (ACTS) at the time of enrolment, the results demonstrate higher overall QoL, as measured by Fact-G.

Finally, the results of the impact of treatment with oral factor Xa inhibitors on the QoL of patients in the EDOI study also suggest the evaluation of the CAT score in clinical practice [14,15]

4.1. Strengths and limitations

The EDOI trial has several limitations. The most relevant is related to the COVID-19 pandemic event which has implied an amendment in the estimation of the sample size, reducing it by half. This amendment, combined with the high heterogeneity of the population study, reduced the robustness of the estimation of all results, especially the primary endpoint and other outcomes with rare (<10 %) occurrence rates. Secondly, the absence of an ad-hoc digital instrument dedicated to a more flexing detection of the PROs measurements during the follow-up has led to a high non-responder rate, which could not be fully explained by deaths.

Nevertheless, the study also has strengths. Indeed, to curb the above limitations, refined statistical models were adopted. Implementing the Fine-Gray model has allowed robust estimation of the incidence of AEs, taking into account the competitive risks of deaths. Last but not least, the use of MMRM models afforded the assessment of the between and within-group differences over repeated measures. This choice was helpful, limiting the issue of missing data in the PROs measurement.

5. Conclusion

In conclusion, the phase IV EDOI study is the first multicentre trial that rigorously evaluated the impact of edoxaban-related AEs on antineoplastic therapy in cancer patients with VTE. The study showed a low impact of edoxaban-related AEs on antineoplastic therapy compliance. The most critical phase in the management of edoxaban was within the first 30 days. Patients who overcome this period drastically reduce the probability of AEs. This study also focused on the PROs measurement, highlighting an interesting trend in QoL scores. Indeed, the significant

Table 2
Multivariable analysis via MMRM models with Fact-G, Pact-Q2 Convenience, Pact-Q2 Satisfaction, ACTS Burden and ACTS Benefit score.

	Fact-G			Pact-Q2: Convenience			Pact-Q2: Satisfaction			ACTS: Burden			ACTS: Benifit		
Fixed Effects															
Predictors	**Estimates**	**95 %CI**	**p-value**	**Estimates**	**95 %CI**	**p-value**	**Estimates**	**95 %CI**	**p-value**	**Estimates**	**95 %CI**	**p-value**	**Estimates**	**95 %CI**	**p-value**
(Intercept)	67.70	63.87 – 71.53	< 0.001	78.97	76.35 – 81.60	< 0.001	52.78	47.95 – 57.61	< 0.001	51.09	49.40 – 52.78	< 0.001	10.24	9.58 – 10.89	< 0.001
at 1 month	1.31	−0.38 – 3.00	0.127	5.07	3.01 – 7.14	< 0.001	3.26	0.74 – 5.78	0.011	1.92	1.00 – 2.84	< 0.001	−0.20	−0.68 – 0.28	0.408
at 3 months	−0.42	−2.46 – 1.63	0.690	5.11	2.66 – 7.55	< 0.001	5.24	2.37 – 8.11	< 0.001	2.01	0.90 – 3.13	< 0.001	−0.30	−0.89 – 0.28	0.311
at 6 months	−1.06	−3.78 – 1.65	0.441	5.37	2.17 – 8.57	0.001	2.57	−1.05 – 6.20	0.163	1.71	0.21 – 3.21	0.025	−0.25	−1.05 – 0.55	0.532
Edoxaban-related AEs	5.89	0.13 – 11.65	0.045	3.90	−1.24 – 9.04	0.136	2.79	−2.23 – 7.80	0.275	1.66	−0.70 – 4.01	0.168	0.20	−0.71 – 1.11	0.667
Diabetes	−6.87	−12.38 – −1.36	0.015				−3.99	−8.57 – 0.59	0.088						
Death occurred during the study	−6.66	−11.07 – −2.25	0.003				3.43	−0.66 – 7.52	0.100						
Male	3.97	−0.37 – 8.31	0.073												
Edoxaban treatment for 6 months							7.23	2.88 – 11.58	0.001	1.65	−0.26 – 3.55	0.091			
Gastric primary tumor site							3.13	−0.46 – 6.73	0.087				1.03	0.30 – 1.76	0.006
Random Effects															
σ2: residual variance	35.82			54.86			85.28			10.79			2.91		
τ00 (id) st.dev within component of cluster id	183.88			229.88			102.50			37.75			4.32		
τ11 (id*Time): st.dev within component of time on cluster id	7.79			12.44			8.12			2.53			0.78		
ρ01 (id): correlation of patients over time	−0.45			−0.78			−0.53			−0.68			−0.62		
ICC: intracluster correlations	0.84			0.81			0.55			0.78			0.60		
N.id: number of patients included in the analysis	141			140			138			140			139		
Observations: number of available patients over time (repeated measures)	386			390			381			389			386		
Marginal R2 / Conditional R2	0.092 / 0.852			0.025 / 0.812			0.083 / 0.583			0.033 / 0.785			0.049 / 0.617		

worsening after 1 month of edoxaban treatment, should suggest to clinicians to pay attention to these frail patients to eventually integrate supportive care.

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CRediT authorship contribution statement

Romagnani Alessandra: Writing – review & editing, Data curation. **Finotto Silvia:** Writing – review & editing, Investigation. **Antonuzzo Lorenzo:** Writing – review & editing, Investigation. **Damato Angela:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Data curation. **Giovanardi Filippo:** Writing – review & editing, Investigation. **Maglietta Giuseppe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Gelsomino Fabio:** Writing – review & editing, Investigation. **Pinto Carmine:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Di Maio Massimo:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Tamberi Stefano:** Writing – review & editing, Investigation. **Gervasi Erika:** Writing – review & editing, Data curation. **Mandarà Marta:** Writing – review & editing, Investigation. **Grisanti Salvatore:** Writing – review & editing, Investigation. **Catino Annamaria:** Writing – review & editing, Investigation. **Montesarchio Vincenzo:** Writing – review & editing, Investigation. **Tiseo Marcello:** Writing – review & editing, Investigation. **Brighenti Matteo:** Writing – review & editing, Investigation.

Declaration of Competing interest

CP: outside the submitted work personal fees for the advisory role, speaker engagements, and travel and accommodation expenses from Amgen, Astellas, AstraZeneca, Bayer, Bristol Meyer Squibb, Celgene, Daiichi Sankyo, , Eisai, Ipsen, Janssen, Incyte, Merck-Serono, Merck Sharp and Dohme, Novartis, Roche, Sandoz, Sanofi, and Servier. **AD:** outside the submitted work, has received personal fees for the advisory role, speaker engagements, and travel and accommodation expenses from Ipsen, Servier, BMS, Merck Serono, Amgen, and Daichii Sankyo. **MT:** received speakers' and consultants' fee from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Takeda, Amgen, Merck, Sanofi, Janssen, Daiichi Sankyo. M.T. received institutional research grants from Astra-Zeneca, Boehringer Ingelheim and Roche. M.T. received travel support from Amgen and Takeda. **FaG:** honoraria for Advisory board/Speaker's bureau: Servier, Eli Lilly, Bristol-Myers Squibb, Iqvia, Merck Serono, Amgen, Pierre-Fabre. **MM:** reports honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme (MSD), Novartis, Roche, Takeda, Viatris, Ipsen for consultancy or participation to advisory boards; direct research funding from Tesaro/GlaxoSmithKline, institutional funding for work in clinical trials/contracted research from Beigene, Exelixis, MSD, Pfizer and Roche. Other authors have no COI..

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115296.

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