



Patient-reported outcomes associated with changing to rivaroxaban for the treatment of cancer-associated venous thromboembolism – The COSIMO study

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Venous thromboembolism (VTE) is a frequent complication of cancer usually managed by anticoagulation therapy [1]. Long-term daily doses of anticoagulation therapy may add to the emotional stress and treatment burden experienced by patients with cancer [2]. Observational data demonstrate that long-term persistence with LMWH therapy is low, suggesting general dissatisfaction among patients possibly because of the inconveniences associated with this therapy [3]. Changing from traditional anticoagulants (low-molecular-weight heparin, fondaparinux, or a vitamin K antagonist) to a guideline recommended direct oral anticoagulant (DOAC) may lessen the treatment burden associated with cancer-associated thrombosis (CAT) [4]. The convenience of a long-term therapy has a positive impact on treatment satisfaction, which can

ultimately improve long-term compliance to, or persistence with, therapy and clinical outcomes [5].

The COSIMO study (NCT02742623) was designed to assess patient-reported treatment satisfaction following a planned change from traditional therapy to rivaroxaban for the treatment of CAT. The rationale and design of this study have been reported previously [6]. It was a prospective, non-interventional, single-arm cohort study enrolling patients from 55 sites in Australia, Canada, and Europe. All patients provided written informed consent. The study was performed in accordance with the provisions of the Declaration of Helsinki and local regulations.

Inclusion criteria were adult patients with active cancer other than fully treated basal-cell or squamous-cell carcinoma of the skin (with

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Table 1

Demographics, clinical and cancer-related characteristics at baseline for the safety and ACTS week 4 analysis sets.

Characteristic, n (%)	Study population (N = 505)	ACTS week 4 Analysis set (N = 381)
Age, years, mean \pm SD	64.0 \pm 11.7	64.2 \pm 11.9
Male gender	225 (44.6)	172 (45.1)
Bodyweight, kg, mean \pm SD	76.7 \pm 17.0	76.6 \pm 16.6
<70	162 (32.1)	126 (33.1)
\geq 70–89	189 (37.4)	145 (38.1)
\geq 90	97 (19.2)	72 (18.9)
Missing	57 (11.3)	38 (10.0)
First available CrCl, mL/min		
<15–<30	4 (0.8)	3 (0.8)
\geq 30–<50	42 (8.3)	31 (8.1)
\geq 50–<80	148 (29.3)	116 (30.4)
\geq 80	234 (46.3)	180 (47.2)
Missing	77 (15.2)	51 (13.4)
Index diagnosis ^a		
DVT only	229 (45.3)	180 (47.2)
Symptomatic	181 (35.8)	145 (38.1)
Incidental	48 (9.5)	35 (9.2)
PE only	188 (37.2)	138 (36.2)
Symptomatic	116 (23.0)	84 (22.0)
Incidental	72 (14.3)	54 (14.2)
PE with DVT	49 (9.7)	37 (9.7)
Symptomatic	34 (6.7)	28 (7.3)
Incidental	15 (3.0)	9 (2.4)
Catheter-associated DVT	38 (7.5)	26 (6.8)
Missing	1 (0.2)	0 (0.0)
Previous VTE (\leq 5 years)	44 (8.7)	34 (8.9)
Known thrombophilia ^a	6 (1.2)	4 (1.0)
Previous major bleeding episode	11 (2.2)	10 (2.6)
Cancer category		
Solid tumour	449 (88.9)	322 (84.5)
Breast	84 (16.6)	66 (17.3)
CNS-glioblastoma	11 (2.2)	10 (2.6)
Head and neck	8 (1.6)	3 (0.8)
Lung	59 (11.7)	40 (10.5)
Gastrointestinal	131 (25.9)	96 (25.2)
Gynaecological	80 (15.8)	56 (14.7)
Genitourinary	58 (11.5)	46 (12.1)
Malignant melanoma	3 (0.6)	2 (0.5)
Sarcoma	5 (1.0)	5 (1.3)
Other	10 (2.0)	8 (2.1)
Haematological malignancy	56 (11.1)	49 (12.9)
Metastatic disease of solid tumours	245 (48.5)	177 (46.5)
ECOG performance status		
0	162 (32.1)	127 (33.3)
1	276 (54.7)	210 (55.1)
2	63 (12.5)	42 (11.0)
Missing	4 (0.8)	2 (0.5)
Status of cancer response		
Complete remission	47 (9.3)	37 (9.7)
Partial remission	38 (7.5)	29 (7.6)
Stable disease	146 (28.9)	108 (28.3)
Relapsed disease/progressive disease	89 (17.6)	66 (17.3)
Not evaluable	35 (6.9)	27 (7.1)
Not done	150 (29.7)	114 (29.9)
Systemic therapy	178 (35.2)	141 (37.0)
Chemotherapy	150 (29.7)	116 (30.4)
Hormonal therapy	18 (3.6)	17 (4.5)
Targeted therapy	15 (3.0)	12 (3.1)
Immunotherapy	15 (3.0)	13 (3.4)
Other	6 (1.2)	4 (1.0)
Radiotherapy	79 (15.6)	69 (18.1)

Abbreviations: ACTS, Anti-Clot Treatment Scale; CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

Note: Characteristics were assessed at the time of enrolment (baseline) unless otherwise stated.

^a Index diagnosis and known thrombophilia refer to the date of diagnosis of the index VTE.

active cancer defined as the diagnosis or treatment of cancer within the previous 6 months or recurrent or metastatic cancer) and an Eastern Cooperative Oncology Group (ECOG) score < 3 . Exclusion criteria included contraindications to rivaroxaban and venous thromboembolic events that occurred while patients were taking anticoagulant therapy. Eligible patients with acute venous thromboembolism who received traditional anticoagulant therapy for ≥ 4 weeks and were changing to rivaroxaban were included. The follow-up period was 6 months, with Anti-Clot Treatment Scale (ACTS) questionnaires completed at baseline and at approximately week 4 and months 3 and 6 for pairwise comparison to mean scores at baseline. The primary outcome was change in ACTS Burdens score between baseline and week 4. The effect size is calculated by dividing the mean difference (MD) by the standard deviation (SD) of difference (e.g. MD/SD = 3.8/6.7 = 0.56). The minimal clinically important difference (MCID) is calculated by multiplying the 0.3 (effect size) by the SD. An effect size of ≥ 0.3 (mean difference) was considered clinically significant. An effect size of 0.2 was considered a small difference, 0.5 a moderate difference, and 0.8 a large difference [7,8]. Details of the study questionnaires have been published previously [6]. The ACTS questionnaire is a patient self-reporting instrument that measures the negative and positive aspects of anticoagulation therapy on separate subscales for 'Burdens' (across 13 questionnaire items including one global item) [6]. Patients express their level of agreement with a statement on a 5-point Likert scale. Scores are reverse-coded during analysis; consequently, higher scores indicate greater patient treatment satisfaction. Observations continued for 6 months or until withdrawal of consent, death, or loss to follow-up.

Patients who received at least one dose of rivaroxaban and who completed the ACTS questionnaire at the timepoint for analysis were included. The null hypothesis was no change in mean ACTS Burdens score between baseline and week 4 in pairwise analysis; a 5% significance level was used for hypothesis testing. The change in the mean ACTS Burdens score was analysed using the Wilcoxon signed-rank test. The assumption of normality was tested using the Shapiro–Wilk test at the 0.10 level of significance. For missing items, imputation to the mean was used where $>50\%$ of the questions (>6 items for ACTS Burdens) were completed.

The study enrolled 509 patients; 505 patients received rivaroxaban and were included in the study population. Patient demographics, general clinical characteristics and cancer-related characteristics (Table 1) were assessed at the time of enrollment (baseline) and were similar between patients included in the study population and the ACTS week 4 analysis set. Overall, 117 (23.2%) patients in the study population discontinued the study prematurely: 59 (11.7%) died, 21 (4.2%) withdrew consent, 17 (3.4%) were lost to follow-up, and 20 (4.0%) had 'other' reasons for premature discontinuation. The majority of patients in the study population changed to rivaroxaban from LMWH therapy ($n = 488$, 96.6%); 8 (1.6%) patients changed from a VKA, and 9 (1.8%) patients from fondaparinux.

Overall, patients received a median of 100 days or 3.3 months (interquartile range of 47–181 days or 1.5–6.0 months) of anticoagulation therapy for their VTE before changing to rivaroxaban. The most common reasons for changing to rivaroxaban were patient-dependent reasons, which included a desire to cease parenteral administration ($n = 136$, 26.9%), improve QoL ($n = 94$, 18.6%), general patient preference ($n = 76$, 15.0%); for 174 (34.5%) patients, it was their physician's decision to change their therapy. Most patients were treated with rivaroxaban for at least 3 months ($n = 457$, 90.5%), and at the end of the observation period, 302 (59.8%) remained on rivaroxaban. The median duration of rivaroxaban treatment was 176 days (interquartile range 105–189 days).

For the ACTS analyses, results from 423 (83.8%) patients were valid for inclusion in the ACTS over time analysis set, 381 (75.4%) in the week 4 analysis set, 341 (67.5%) in the month 3 analysis set, and 253 (50.1%) in the month 6 analysis set. Mean ACTS Burdens scores were significantly higher at week 4 compared with baseline (55.6 vs 51.8 out of a

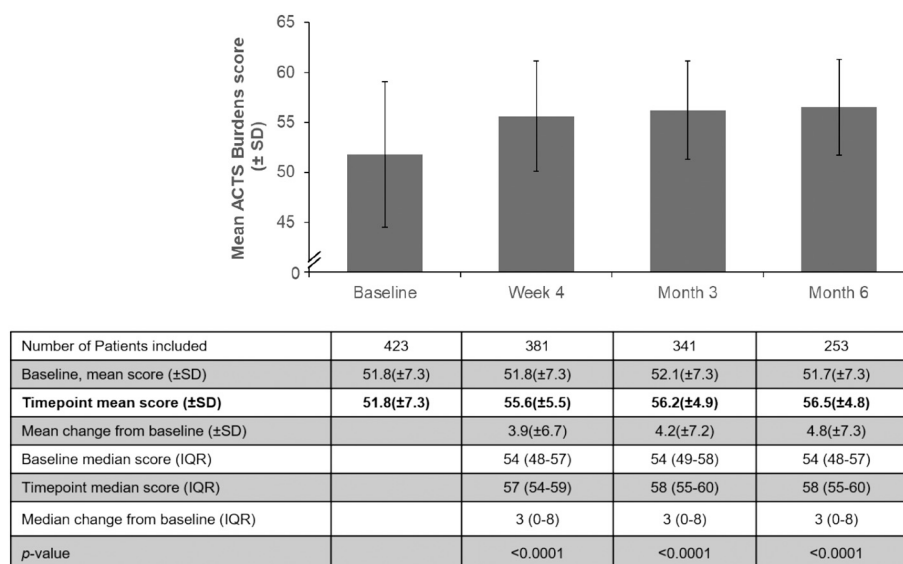


Fig. 1. Patient-reported treatment satisfaction on the ACTS Burdens subscale at week 4 (primary outcome), month 3 and month 6 following a change to rivaroxaban. ACTS, Anti-Clot Treatment Scale; SD, standard deviation.

maximum score of 60, respectively; $p < 0.0001$; effect size 0.6) in the ACTS week 4 analysis set ($N = 381$ patients), signifying a clinically significant increase in treatment satisfaction. This result persisted at months 3 and 6 (Fig. 1).

The minimal clinically important difference (MCID) was 2.0. (0.3 (min. sig. effect size) times 6.71 (SD)). 59.3% (226/381) of patients achieved a MCID by week 4. It is noteworthy that 47% (179/381) and 22% (84/381) of the patients reported ACTS baseline score of ≥ 58 and 60 respectively, suggesting that patient-reported treatment satisfaction increased at week 4 despite almost half of the patient cohort having a high satisfaction score at baseline.

A sensitivity analysis on the ACTS Burden score at Week 4 was conducted to investigate the potential impact on the study outcome of patients who dropped out from the study earlier than Week 4 due to other reasons than death due to cancer. The mean (SD) ACTS Burden subscale was 51.7 (7.31) at baseline, which increased by 3.0 (8.96) to 54.7 (8.22) at Week 4. The median increased from 54.0 to 57.0 by a median of 2.6. The increase was statistically significant. Thus, the sensitivity analysis confirmed the primary outcome and shows that patients that dropped out had no significant impact on the primary outcome.

Data describing patient satisfaction with DOACs for the treatment of CAT are limited. The primary outcome was met with a significant improvement in patient treatment satisfaction on the ACTS Burdens subscale observed at week 4 following a change from LMWH, fondaparinux, or a VKA to rivaroxaban. The significant improvement from baseline persisted at months 3 and 6. The almost immediate increase in treatment satisfaction observed at week 4 is strongly supportive of the treatment-dependent nature of the change in satisfaction.

The improvement in ACTS Burdens score at week 4 (a mean difference of 3.9) was similar to previously reported differences in ACTS Burdens scores in head-to-head comparisons of rivaroxaban and VKA therapy for the treatment of VTE [7,8]. The effect size in COSIMO of 0.6 was considered to be a clinically significant change, while the mean differences in the EINSTEIN DVT and EINSTEIN PE trials were equivalent to moderate effect sizes of 0.4 and 0.5, respectively [7,8].

The COSIMO study utilised a non-interventional approach; therefore, patient-reported outcomes were representative of patients with CAT who are likely to be selected for rivaroxaban therapy in routine practice. Similar to other trials, approximately half of patients enrolled in the current study had metastases and $\sim 90\%$ had solid tumours [9].

However, fewer patients received concomitant systemic anticancer therapy and/or radiotherapy (42.8% in the COSIMO study, compared with 72.4 and 69.5% of patients in the Hokusai-VTE-Cancer and SELECT-D trials, respectively) [9]. Although a major limitation of this study is its single-arm study design, a non-randomised two-armed design, comparing outcomes in patients changing to rivaroxaban with those persisting with traditional anticoagulants, builds in inherent bias in addition to confounders that cannot be overcome or mitigated with statistical adjustment.

Several factors in the study design may have potentially influenced the reported patient satisfaction score. Firstly, patients selected were likely to be dissatisfied with their current treatment regimen, which may have led to an overestimation of patient satisfaction after treatment change. However, our findings were consistent with a recent study assessing treatment satisfaction switching from vitamin K antagonists to DOACs [10]. Although baseline ACTS Burdens scores were high, a statistically and clinically significant improvement in ACTS Burdens score was continuously observed at all timepoints of measure. Secondly, the numbers of patients included in each timepoint analysis should be considered. There were 423 patients at baseline (100.0%) who had a completed and valid ACTS questionnaire and 381 patients (90.1%) at Week 4. Patients who discontinued prematurely, including those who died, might have experienced different treatment satisfaction to those who remained in the study. Regardless, according to the sensitivity analysis of the ACTS results, a noticeable improvement in treatment satisfaction was still observed at week 4 when baseline scores from patients who had discontinued early from the study including those who died for reasons other than cancer were included.

General limitations of the study include patients being surveyed in writing and by telephone might bias the types of patients participating. Patient satisfaction is a subjective measurement and the possibility that some patients misinterpreted the questionnaires cannot be excluded. Of note, because 96.6% of patients changed from LMWH therapy, the primary driver for the improvement in patient satisfaction may be the change from an injectable to an oral agent. Finally, the geographical distribution of the study was limited to Europe, Canada, and Australia.

The COSIMO study demonstrates that patients with CAT who changed their VTE treatment from LMWH, fondaparinux, or VKA therapy to rivaroxaban in everyday clinical practice experienced an improvement in treatment satisfaction, in reducing patient-reported anticoagulation burden. Improved treatment satisfaction following a

change to rivaroxaban for the treatment of CAT has conceivable positive implications for long-term persistence with therapy and clinical outcomes.

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CRedit author contribution statement

The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the manuscript, and its final contents.

Declaration of competing interest

ATC reports personal fees from Bayer and Janssen during the conduct of the study; grants and personal fees from Bristol Myers Squibb, Daiichi Sankyo Europe, and Pfizer, and personal fees from AbbVie, Boehringer Ingelheim, Exxom Group, ONO Pharmaceuticals and Portola Pharmaceuticals, outside the submitted work. AM reports grants and personal fees from Bayer, during the conduct of the study; grants and personal fees from Bristol Myers Squibb, and personal fees from LEO Pharma, outside the submitted work. JB-W reports grants and personal fees from Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo and Pfizer, and personal fees from CSL Behring and LEO Pharma, outside the submitted work. AYYL reports personal fees from Bayer, during the conduct of the study; grants from Bristol Myers Squibb, personal fees from LEO Pharma and Pfizer, outside of the submitted work. KF, KA, SF, LB, and MB are employees of Bayer AG. YD is an employee of Bayer US LLC. LGM reports personal fees from Bayer, research funding from Bayer, Boehringer Ingelheim and Daiichi Sankyo outside the submitted work and support from the Italian Ministry of Health, Ricerca Corrente IRCCS Multimedica during the conduct of the study.

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Appendix A. Supplementary data

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