Analysis of patients with deep vein thrombosis switched from standard therapy to rivaroxaban in the non-interventional XALIA study

Alexander G.G. Turpie, Lorenzo G. Mantovani, Sylvia Haas, Reinhold Kreutz, Danja Monje, Jonas Schneider, Martin van Eickels, Martin Gebel, Walter Ageno

PII: S0049-3848(17)30255-4
DOI: doi: 10.1016/j.thromres.2017.04.001
Reference: TR 6617

To appear in: *Thrombosis Research*

Received date: 16 November 2016
Revised date: 29 March 2017
Accepted date: 2 April 2017

Please cite this article as: Alexander G.G. Turpie, Lorenzo G. Mantovani, Sylvia Haas, Reinhold Kreutz, Danja Monje, Jonas Schneider, Martin van Eickels, Martin Gebel, Walter Ageno , Analysis of patients with deep vein thrombosis switched from standard therapy to rivaroxaban in the non-interventional XALIA study. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Tr(2017), doi: 10.1016/j.thromres.2017.04.001

Analysis of patients with deep vein thrombosis switched from standard therapy to rivaroxaban in the non-interventional XALIA study

Alexander G.G. Turpie,[a] Lorenzo G. Mantovani,[b] Sylvia Haas,[c] Reinhold Kreutz,[d] Danja Monje,[e] Jonas Schneider,[f] Martin van Eickels,[f] Martin Gebel[g] and Walter Ageno[h]

[a]Department of Medicine, Hamilton Health Sciences, Hamilton, Ontario, Canada
[b]CESP-Center for Public Health Research, University of Milan Bicocca, Monza, Italy
[c]Vascular Centre, Munich, Germany
[d]Institute of Clinical Pharmacology and Toxicology, Charité Universitätsmedizin, Berlin, Germany
[e]Bayer Vital GmbH, Leverkusen, Germany
[f]Bayer AG, Berlin, Germany
[g]Bayer AG, Wuppertal, Germany
[h]Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy

Contact information for corresponding author:
Alexander G.G. Turpie
19 Brant Street, Suite 802
Toronto, Ontario, Canada M5V 2L2
Phone no: +1 905 929 4385
Email: turpiea@mcmaster.ca

Word count: 3331
No. of tables: 2
No. of figures: 2
No. of references: 8

Abstract

Introduction

XALIA assessed the safety and effectiveness of rivaroxaban for deep vein thrombosis (DVT) treatment in routine clinical practice. This substudy describes the clinical characteristics and outcomes of 'early switchers' – patients who received heparin or fondaparinux for >2–14 days and/or a vitamin K antagonist (VKA) for 1–14 days before switching to rivaroxaban.

Materials and Methods

Patients with DVT (latterly with concomitant pulmonary embolism) received rivaroxaban or standard anticoagulation (initial treatment with heparin or fondaparinux, usually overlapping with and followed by a VKA). Patients administered rivaroxaban alone, or heparin or fondaparinux for ≤48 hours pre-enrolment were included in the rivaroxaban cohort. Therapy type, dose, and duration were at the physician's discretion. Primary outcomes were major bleeding, recurrent venous thromboembolism (VTE), and all-cause mortality.

Results

In 368 early switchers, recurrence or bleeding risk factors were more prevalent versus the rivaroxaban cohort, including creatinine clearance <50 mL/min (6.5% vs. 3.9%), previous major bleeding (4.6% vs. 1.4%), active cancer (8.2% vs. 5.6%), and concomitant pulmonary embolism (20.9% vs. 8.4%). Crude incidence rates were numerically higher versus the rivaroxaban cohort for major bleeding (1.4% vs. 0.7%), recurrent VTE (2.2% vs. 1.4%), and all-cause mortality (0.8% vs. 0.5%).

Conclusions

Patients who switched to rivaroxaban early in the treatment process had a higher frequency of risk factors for bleeding and recurrent VTE than patients treated with rivaroxaban; reflected by the higher risk of adverse events in that group during follow-up.

Abstract word count: 235/250

Keywords:

Anticoagulant
Non-interventional study
Rivaroxaban
Therapy switch
Venous thromboembolism

Trial registration number: NCT01619007

Abbreviations

CNS, central nervous system; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; Q, quartile; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Highlights

- ‘Early switchers’ received rivaroxaban after prolonged parenteral/VKA therapy
- They had more VTE recurrence risk factors than the rivaroxaban cohort
- The crude incidence rates for the primary outcomes reflected this difference
- Hospital stay duration was also longer for early switchers

Introduction

The efficacy and safety of rivaroxaban for venous thromboembolism (VTE) treatment have been demonstrated in the EINSTEIN DVT and EINSTEIN PE phase III trials [1,2]. XALIA, a multicenter, non-interventional study, assessed the safety and effectiveness of the single-drug approach with rivaroxaban for the treatment of deep vein thrombosis (DVT) versus standard anticoagulation therapy in routine clinical practice [3]. Patients with DVT and concomitant pulmonary embolism (PE) were also included after the approval of rivaroxaban in the PE indication. Of the 5142 eligible patients enrolled in XALIA, 5136 received anticoagulation therapy; treatment decisions (including dose and duration of therapy) were at the physician's discretion. The findings of XALIA were consistent with those from the phase III EINSTEIN trials, with low rates of major bleeding and recurrent VTE observed in both the rivaroxaban and standard anticoagulation groups.

The aim of the XALIA study was to compare rivaroxaban, administered as a single-drug approach in accordance with the EINSTEIN DVT protocol, to standard anticoagulation [1]. Because XALIA was a real-world study, it was observed that physicians elected to prolong standard anticoagulation in some patients before switching to rivaroxaban. In contrast, patients in EINSTEIN DVT who received parenteral treatment for >48 hours before receiving rivaroxaban were not eligible; thus evidence on the safety and efficacy of this approach is lacking. Therefore, in XALIA, a third group termed 'early switchers' emerged in the course of the study; the group was defined in order to adequately address this real-world observation. Early switchers were those patients who received heparin or fondaparinux for >2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban.

Because the early switchers were excluded *a priori* from the XALIA safety analysis, they were considered separately. The purpose of this post hoc descriptive analysis was, therefore, to describe the outcomes data, clinical characteristics and treatment patterns for this patient cohort.

Methods

The methods were described in detail in the XALIA study primary manuscript [3].

Study design and participants

XALIA was a multicenter, international, prospective, non-interventional study of patients with DVT that took place in 19 European countries, Israel and Canada. Patients received

rivaroxaban or standard anticoagulation (initial treatment with unfractionated heparin, low molecular weight heparin, or fondaparinux, usually overlapping with and followed by a VKA). Patients could be included if they were aged 18 years or older with objectively confirmed DVT and an indication to receive anticoagulation treatment for at least 3 months. Following the approval of rivaroxaban in the PE indication, the protocol was amended to allow the enrolment of patients with DVT and concomitant PE (but not isolated PE).

Procedures

Treatment, dose, and duration were at the attending physician's discretion. For the primary analysis of this study, patients who received rivaroxaban alone and those who had received heparin or fondaparinux for a maximum of 48 hours before enrollment and then administered rivaroxaban were included in the rivaroxaban cohort, consistent with the approach used in EINSTEIN DVT [1]. Early switchers were those patients who initially received heparin or fondaparinux for >2–14 days and/or a VKA (with or without heparin or fondaparinux) for 1–14 days before switching to rivaroxaban. Patients who switched after the 14-day threshold were included in their original therapy group for analysis purposes. The analyses are presented as an 'on-treatment' analysis, i.e. events are assigned to the treatment (rivaroxaban or standard anticoagulation) that was given initially after the index event. Only events occurring while on this initial treatment are considered as 'on treatment'. For the early switchers, only events occurring while on rivaroxaban are considered.

Outcomes

The primary outcomes in XALIA were major bleeding, recurrent VTE and all-cause mortality. Major bleeding was defined as: overt bleeding associated with a fall in hemoglobin of 20 g/L or more; a transfusion of two or more units of packed red blood cells or whole blood; critical site bleeding (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal); or fatal bleeding. Recurrent VTE was defined as the new onset of symptoms confirmed by objective diagnostic testing. Death was classified as VTE-related, bleeding-related, or from other causes.

Secondary outcomes were: major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction, unstable angina, acute coronary syndrome); other symptomatic thromboembolic events (Budd–Chiari syndrome, retinal-vein thrombosis, sinus-vein thrombosis, portal-vein thrombosis, catheter-associated thrombosis, upper-limb thrombosis [if initial DVT was not an upper-limb thrombosis]); healthcare resource use (admissions to hospital and length of stay); and other adverse events.

All outcomes, including cause of death, were centrally adjudicated.

Statistical analysis

A descriptive analysis was conducted comparing the crude rates for the primary outcomes for the three treatment groups (rivaroxaban, standard anticoagulation, early switchers).

Results

Baseline demographics and clinical characteristics

A total of 5142 patients were enrolled between 26 June 2012 and 31 March 2014; 6 patients did not take study medication and were excluded from the analysis. Of the remaining 5136 patients, 2619 (51.0%) received rivaroxaban in accordance with the EINSTEIN DVT study protocol, 2149 (41.8%) received standard anticoagulation, and 368 (7.2%) were early switchers. Figure 1 shows the flow of patients through the study.

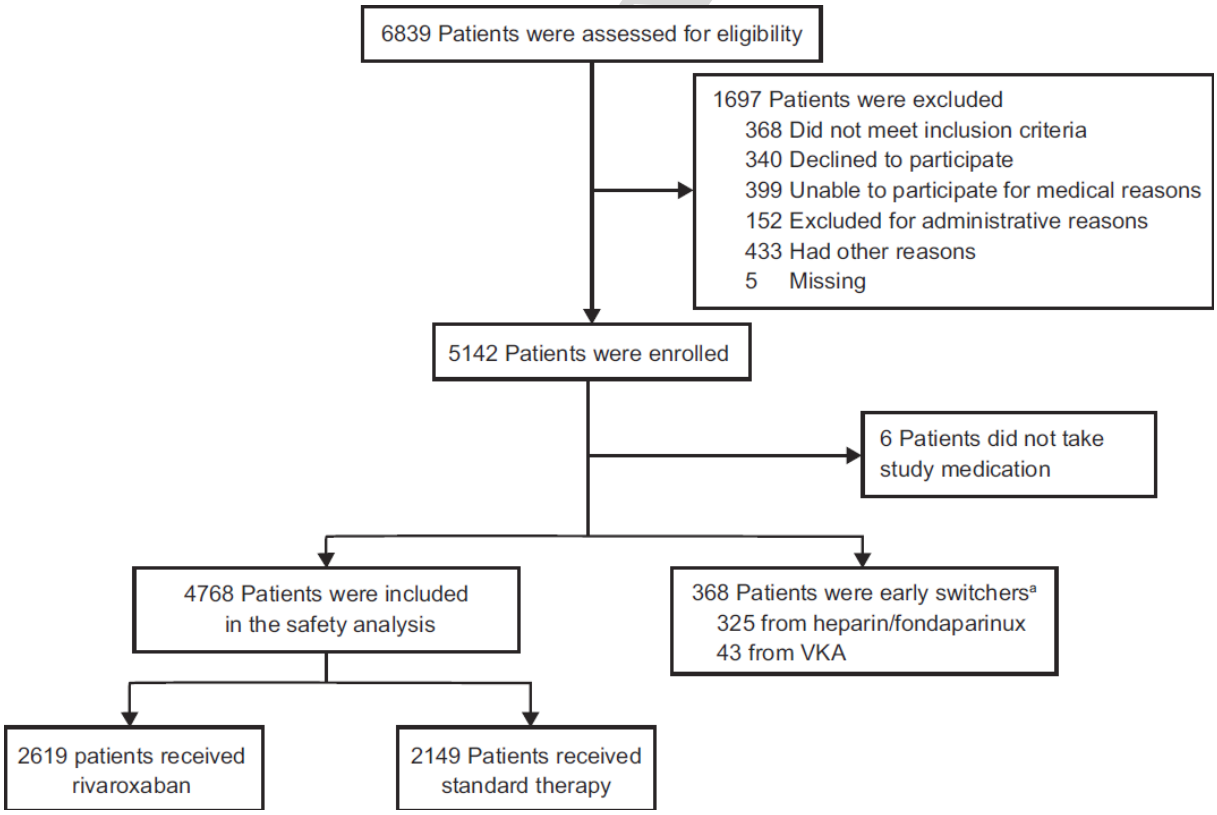

Fig. 1

Trial profile. [a]Early switchers were defined as patients for whom rivaroxaban was planned, but who initially received heparin or fondaparinux for at least 2–14 days, a vitamin K

antagonist for 1–14 days, or both before switching to rivaroxaban. 116 patients in the rivaroxaban group and 128 in the standard anticoagulation group were lost to follow-up.

Of the 368 early switchers, 325 (88.3%) received heparin or fondaparinux only, and 43 (11.7%) received a VKA (with or without heparin or fondaparinux) before starting rivaroxaban. The numbers of patients switching to rivaroxaban per day are shown in Figure 2. Days 3 and 4 after the start of treatment had the highest numbers of patients switching to rivaroxaban (91 and 80 patients, respectively). The median time to first switch was 4.0 days for both the heparin or fondaparinux and VKA groups.

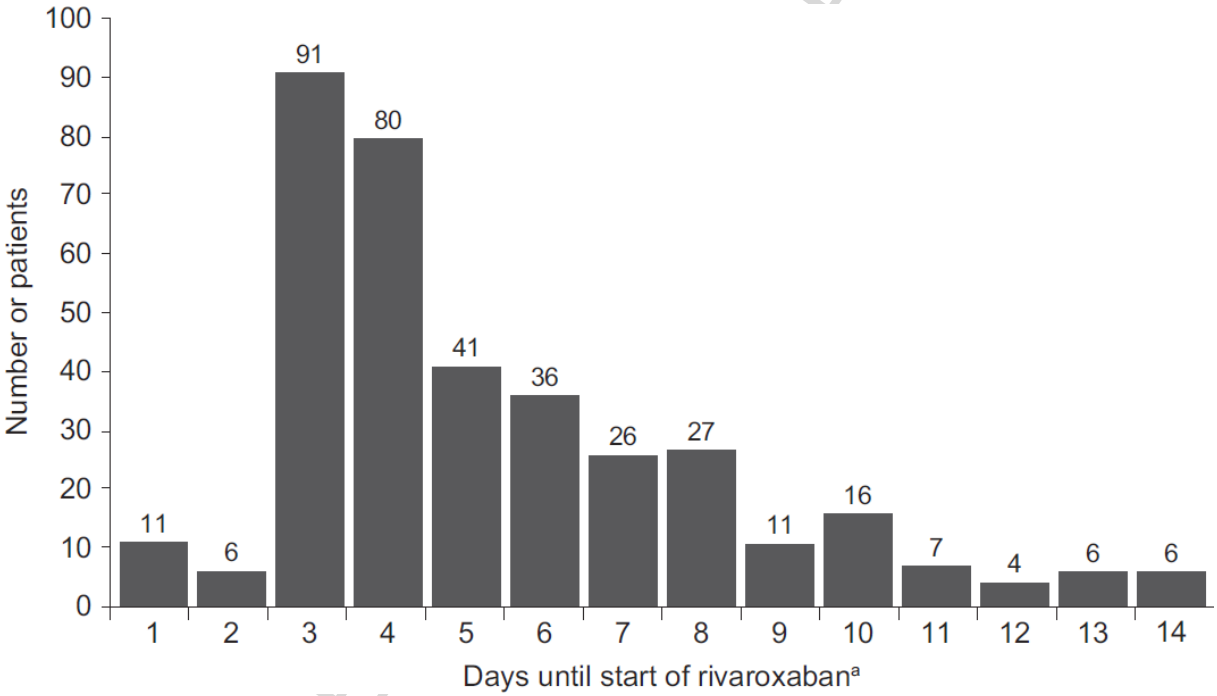

Fig. 2

Number of early switcher patients switching to rivaroxaban per day. [a]Patients who started rivaroxaban on days 1 and 2 were switchers from VKAs.

The median treatment duration on rivaroxaban for early switchers was 190 days (interquartile range [IQR] 107–376 days) compared with a median treatment of 181 days (IQR 94–310 days) in the rivaroxaban group and 190 days (IQR 97–368 days) in the standard anticoagulation group. Fourteen of 368 (3.8%) early switchers were lost to follow-up.

Baseline demographics and clinical characteristics for the three treatment groups are shown in Table 1. The early switchers were more likely to have had a previous major bleeding episode than patients treated with rivaroxaban or standard anticoagulation, and also more frequently concomitant PE.

Table 1

Baseline demographics and clinical characteristics

Characteristic[a]	Rivaroxaban group (n=2619)	Standard anticoagulation group[b] (n=2149)	Early switchers (n=368)
Age (years)	57·3±16·7	63·0±16·9	59·3±17·0
Age category			
<60 years	1366 (52·2%)	824 (38·3%)	172 (46·7%)
≥60 years	1253 (47·8%)	1325 (61·7%)	196 (53·3%)
Male sex	1428 (54·5%)	1116 (51·9%)	211 (57·3%)
Weight			
<50 kg	22 (0·8%)	34 (1·6%)	2 (0·5%)
≥50 to 70 kg	525 (20·0%)	505 (23·5%)	75 (20·4%)
>70 kg to <90 kg	881 (33·6%)	713 (33·2%)	131 (35·6%)
≥90 kg	636 (24·3%)	500 (23·3%)	93 (25·3%)
Missing	555 (21·2%)	397 (18·5%)	67 (18·2%)
First available creatinine clearance			
<30 mL/min	13 (0·5%)	61 (2·8%)	4 (1·1%)
30 to <50 mL/min	88 (3·4%)	157 (7·3%)	20 (5·4%)
50 to <80 mL/min	419 (16·0%)	398 (18·5%)	71 (19·3%)
≥80 mL/min	1125 (43·0%)	797 (37·1%)	169 (45·9%)
Missing	974 (37·2%)	736 (34·2%)	104 (28·3%)
Index diagnosis			
DVT only	2399 (91·6%)	1894 (88·1%)	291 (79·1%)
DVT with PE	220 (8·4%)	255 (11·9%)	77 (20·9%)
Type of VTE[c]			
Provoked	896 (34·2%)	823 (38·3%)	126 (34·2%)
Unprovoked	1692 (64·6%)	1300 (60·5%)	232 (63·0%)
Missing	31 (1·2%)	26 (1·2%)	10 (2·7%)

Characteristic[a]	Rivaroxaban group (n=2619)	Standard anticoagulation group[b] (n=2149)	Early switchers (n=368)
Previous VTE	630 (24·1%)	481 (22·4%)	79 (21·5%)
Active cancer at baseline	146 (5·6%)	411 (19·1%)	30 (8·2%)
Known thrombophilic condition	157 (6·0%)	112 (5·2%)	25 (6·8%)
Previous major bleeding episode	37 (1·4%)	64 (3·0%)	17 (4·6%)

[a]Plus–minus values are means ± SD. [b]Standard anticoagulation consisted of initial treatment with unfractionated heparin, low molecular weight heparin, or fondaparinux, which could overlap with and be followed by an oral vitamin K antagonist. [c]Cancer was not considered when defining DVT as provoked or unprovoked.

DVT, deep-vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

Dosing patterns

The majority of early switchers received rivaroxaban in accordance with the label; 309/368 (84.0%) received an initial dose of 15 mg twice daily; 214/368 (58.2%) had a planned switch to a dose of 20 mg once daily after 21 days. In addition, 74/368 (20.1%) had at least one rivaroxaban dose switch (other than the planned switch at 21 days). The most common among the other reported initially used dosing regimens was 20 mg once daily (24/325 [7.4%] patients in the heparin or fondaparinux only group and 9/43 [20.9%] in the VKA group).

Primary outcomes (crude event rates)

Event rates for all three outcomes were highest in the standard anticoagulation group (this was expected owing to baseline characteristics such as higher mean age and higher rates of cancer in this group) (Table 2). The event rates for the early switchers were intermediate between the rivaroxaban and standard anticoagulation groups. Major bleeding occurred in 5/368 (1.4%, 95% confidence interval [CI] 0.44–3.14) patients in the early switcher group, compared with 19/2619 (0.7%, 95% CI 0.44–1.13) patients in the rivaroxaban group and 48/2149 (2.2%, 95% CI 1.65–2.95) patients in the standard anticoagulation group. In total, 8/368 (2.2%, 95% CI 0.94–4.24) recurrent venous thromboembolic events occurred in the early switcher group, compared with 37/2619 (1.4%, 95% CI 1.00–1.94) in the rivaroxaban group and 55/2149 (2.6%, 95% CI 1.93–3.32) in the standard anticoagulation group. All-cause mortality occurred in 3/368 (0.8%, 95% CI 0.17–2.36) patients in the early switcher group, compared with 12/2619 (0.5%, 95% CI 0.24–0.80) patients in the rivaroxaban group and 88/2149 (4.1%, 95% CI 3.30–5.02) patients in the standard anticoagulation group. A detailed description of the primary outcomes is shown in Table 2.

Table 2

Treatment-emergent clinical outcomes.

	Rivaroxaban group (n=2619)	Standard anticoagulation group (n=2149)	Early switchers (n=368)
Safety			
Major bleeding episode (adjudicated)			
Any	19 (0.7%)	48 (2.2%)	5 (1.4%)
Fatal	0 (0.0%)	2 (0.1%)	0 (0.0%)
Gastrointestinal	3 (0.1%)	18 (0.8%)	2 (0.5%)
CNS (intracranial, subdural, subarachnoid, or cerebral)	6 (0.2%)	5 (0.2%)	0 (0.0%)
Any investigator-reported bleeding (unadjudicated)	298 (11.4%)	218 (10.1%)	42 (11.4%)
Adverse event			
Any event emerging during treatment	944 (36.0%)	805 (37.5%)	143 (38.9%)
Any serious event emerging during treatment	278 (10.6%)	388 (18.1%)	49 (13.3%)
Any event resulting in discontinuation of study drug	157 (6.0%)	120 (5.6%)	22 (6.0%)
Any event leading to or prolonging hospitalization	235 (9.0%)	318 (14.8%)	58 (15.8%)
Effectiveness			
Recurrent VTE	37 (1.4%)	55 (2.6%)	8 (2.2%)
Type of recurrent VTE			
Fatal PE	1 (<0.1%)	1 (<0.1%)	0 (0.0%)

Death in which PE could not be ruled out	4 (0.2%)	4 (0.2%)	1 (0.3%)
Non-fatal PE	17 (0.6%)	17 (0.8%)	3 (0.8%)
Recurrent DVT plus PE	1 (<0.1%)	4 (0.2%)	0 (0.0%)
Recurrent DVT	13 (0.5%)	30 (1.4%)	4 (1.1%)
Other	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Other			
Major adverse cardiovascular events	9 (0.3%)	13 (0.6%)	4 (1.1%)
Other thromboembolic events	4 (0.2%)	5 (0.2%)	0 (0.0%)
All-cause mortality	12 (0.5%)	88 (4.1%)	3 (0.8%)
Cause of death			
VTE-related death			
PE	1 (<0.1%)	1 (<0.1%)	0 (0.0%)
PE not ruled out	3 (0.1%)	3 (0.1%)	1 (0.3%)
Bleeding related	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cancer related	6 (0.2%)	61 (2.8%)	0 (0.0%)
Cardiovascular disease	1 (<0.1%)	10 (0.5%)	1 (0.3%)
Other	1 (<0.1%)	13 (0.6%)	1 (0.3%)

CNS, central nervous system; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Secondary outcomes

Four of 368 patients (1.1%) in the early switcher group had a major adverse cardiovascular event, compared with 9/2619 (0.3%) patients in the rivaroxaban group and 13/2149 (0.6%) patients in the standard anticoagulation group. With regards to the occurrence of other symptomatic thromboembolic events (i.e. venous thrombosis occurring in other sites), there were no events in the early switcher group, 4 (0.2%) in the rivaroxaban group and 5 (0.2%) in the standard anticoagulation group.

Of the 368 patients in the early switcher group, 208 (56.5%) were hospitalized, compared with 727/2619 (27.8%) patients in the rivaroxaban group and 1011/2149 (47.0%) patients in the standard anticoagulation group. The median length of stay for hospitalized patients was 7 days (IQR 5–10 days) for the early switcher group versus 5 days (IQR 3–7 days) for patients in the rivaroxaban group and 8 days (IQR 5–11) for patients in the standard anticoagulation group. Data on patient-reported treatment satisfaction will be reported separately.

Discussion

In XALIA, 7.2% of patients were early switchers; this is an important patient group, because they are indicative of the type of decision-making that occurs in real-world clinical practice – where patients perceived to be at higher risk sometimes receive standard anticoagulation for a few days, before therapy with a novel oral anticoagulant is started. The findings suggest that physicians prescribed standard anticoagulation to many fragile/higher-risk patients before starting rivaroxaban, which is supported by the baseline demographic and clinical characteristic data. For example, a higher proportion of early switcher patients had concomitant PE compared with the rivaroxaban group. The baseline data also show that patients in the early switcher group were more likely to have a prior major bleeding episode than patients in the rivaroxaban and standard anticoagulation groups. Patients in the early switcher group were intermediate between the rivaroxaban and standard anticoagulation groups in terms of age and the proportion of patients with cancer at baseline. Consistent with the baseline demographics and clinical characteristics, the crude rates for the primary outcomes in the early switchers were numerically higher than in the rivaroxaban group and numerically lower than in the standard anticoagulation group.

Patients in the early switcher group were more often hospitalized than patients treated with rivaroxaban or standard anticoagulation, but they had a shorter median stay duration than patients treated with standard anticoagulation (7 vs. 8 days). Dosing was largely in

accordance with the rivaroxaban label (15 mg twice daily for 21 days followed by 20 mg once daily thereafter), although other dosing patterns were seen in some patients in the initial 21-day phase; the most common dosing regimen was 20 mg once daily. Dose ranging studies in patients with VTE comparing 20, 30, and 40 mg once-daily doses of rivaroxaban have shown that the lowest effective daily dose of rivaroxaban was 20 mg [4,5].

In clinical practice, there are a variety of reasons why patients switch anticoagulation therapy [6]. The facilitation of outpatient management is streamlined with non-VKA oral anticoagulants compared with parenteral agents. Therapy failure, drug intolerance, and patient preference can also result in switching. Many physicians are also understandably cautious with use of novel oral anticoagulant drugs, particularly in patients with a higher risk profile, and are more comfortable initially administering more familiar therapies. In many countries, the reimbursement status of rivaroxaban may also have contributed to the number of ‘early switchers’.

A pooled analysis of the EINSTEIN DVT and EINSTEIN PE phase III trials demonstrated that fragile patients, patients with cancer, and patients with a previous VTE showed a significant net clinical benefit with rivaroxaban versus standard anticoagulation [7,8]. The XALIA early switcher results indicated that physicians often administered standard anticoagulation to patients fitting these descriptions; as highlighted in the discussion of reasons for switching, this may have been due to caution over use of a novel therapy (additionally, the EINSTEIN subgroup analyses were published during the course of the XALIA study, meaning that the data were not available when the choice of treatment to initiate was made for some patients). Switching to rivaroxaban in XALIA did not appear to adversely affect treatment outcomes, despite the greater presence of risk factors in early switchers versus patients in the rivaroxaban cohort.

A limitation of this analysis is the small sample size, although it was expected that relatively few patients would fall into the early switcher category (particularly as those switching to rivaroxaban from heparin or fondaparinux within 48 hours were categorized as part of the rivaroxaban cohort, consistent with the EINSTEIN DVT study protocol) [1]. The open-label nature of the study could introduce bias, for example for adverse event reporting. However, the blinding of the adjudication committee to treatment choice helped to reduce this for the adjudication of recurrent VTE, death and major bleeding events. Finally, although most patients received rivaroxaban in accordance with the label, some received different dosing regimens; the reasons for this are unclear because of the small size and heterogeneity of the latter group.

The findings of this study suggest that patients who switched from standard anticoagulation to rivaroxaban early in the treatment process had a higher frequency of risk factors for bleeding and recurrent VTE than patients treated with rivaroxaban from the beginning of the study. This was reflected in the higher risk of adverse events during follow-up.

Acknowledgements and disclosures

Contributors

AGGT created the initial draft of this report. WA, LGM, SH, RK, and AGGT were members of the adjudication committee. MG performed the statistical analysis. All authors participated in writing and reviewing the report and accept full responsibility for its overall content.

Declaration of interests

AGGT has received speaker's honoraria and consultancy fees from, and participated in scientific advisory boards for, Bayer and Janssen Research & Development, LLC. LGM has received consultancy fees from Bayer and Daiichi Sankyo, and research support from Boehringer Ingelheim, Janssen-Cilag Ltd, and Pfizer Inc. SH has received consultancy fees from Aspen Pharmacare, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer Inc., and Sanofi SA. RK has received consultancy fees from Bayer, Berlin-Chemie Menarini, Daiichi Sankyo, Lundbeck Ltd, and Servier Laboratories Ltd, and speaker's honoraria from Bayer, Bristol-Myers Squibb, and Daiichi Sankyo. DM, JS, MvE, and MG are employees of Bayer AG. WA has received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb-Pfizer, and Daiichi Sankyo, and has received research support from Bayer.

Acknowledgments

The information contained in this article is presented on behalf of the XALIA Investigators
The study was funded by Bayer AG and Janssen Research & Development, LLC. We thank Robert Gillies (medical writer) of Chameleon Communications International, UK, who provided editorial assistance funded by Bayer AG and Janssen Scientific Affairs, LLC.

References

[1] The EINSTEIN Investigators, Oral rivaroxaban for symptomatic venous thromboembolism, N. Engl. J. Med. 363 (2010) 2499–2510.

[2] The EINSTEIN–PE Investigators, Oral rivaroxaban for the treatment of symptomatic pulmonary embolism, N. Engl. J. Med. 366 (2012) 1287–1297.

[3] W.Ageno, L.G.Mantovani, S.Haas, R.Kreutz, D.Monje, J.Schneider, et al., Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study, Lancet Haematol 3 (2016) e12–e21.

[4] G.Agnelli, A.Gallus, S.Z.Goldhaber, S.Haas, M.V.Huisman, R.D.Hull, et al., Treatment of proximal deep-vein thrombosis with the oral direct Factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with acute symptomatic Deep-Vein Thrombosis) study, Circulation 116 (2007) 180–187.

[5] H.R.Buller, A.W.A.Lensing, M.H.Prins, G.Agnelli, A.Cohen, A.S.Gallus, et al., A dose-ranging study evaluating once-daily oral administration of the Factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study, Blood 112 (2008) 2242–2247.

[6] C.H.Yeh, P.L.Gross, J.I.Weitz, Evolving use of new oral anticoagulants for treatment of venous thromboembolism, Blood 124 (2014) 1020–1028.

[7] M.H.Prins, A.W.A.Lensing, T.A.Brighton, R.M.Lyons, J.Rehm, M.Trajanovic, et al., Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials, Lancet Haematol. 1 (2014) e37–e46.

[8] M.H.Prins, A.W.A.Lensing, R.Bauersachs, B.van Bellen, H.Bounameaux, T.A.Brighton, et al., Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies, Thromb. J. 11 (2013) 21.

Figure 3

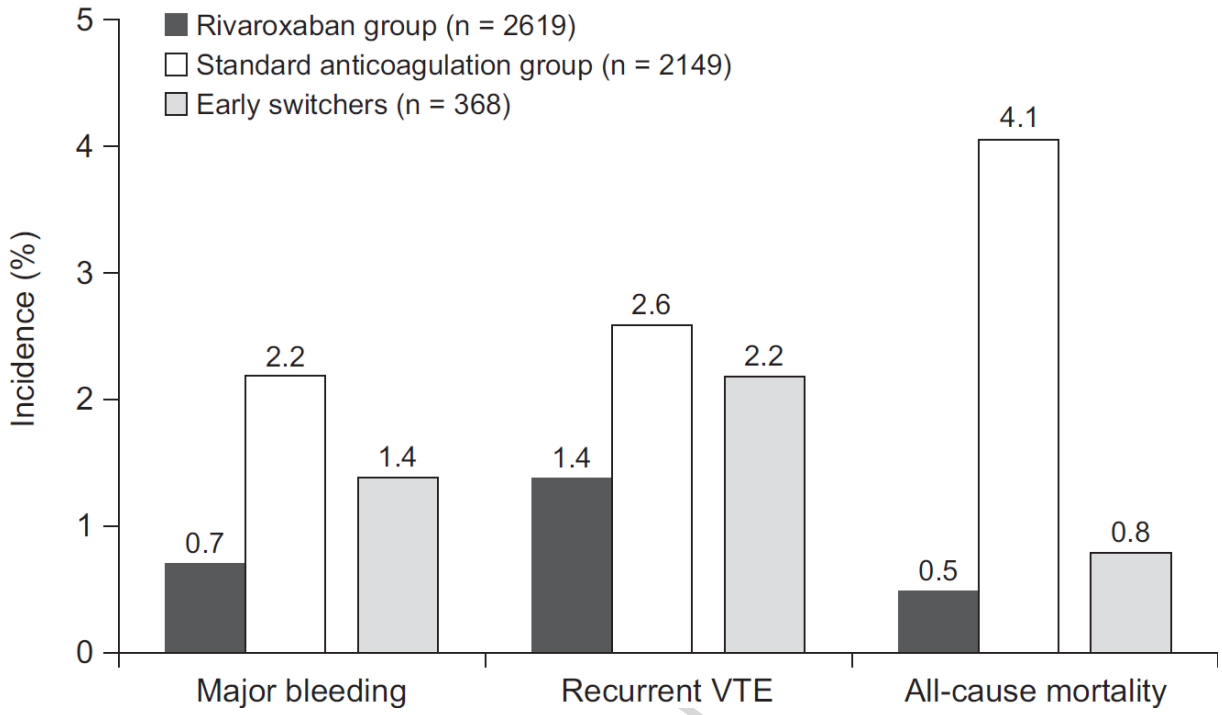

Figure 4

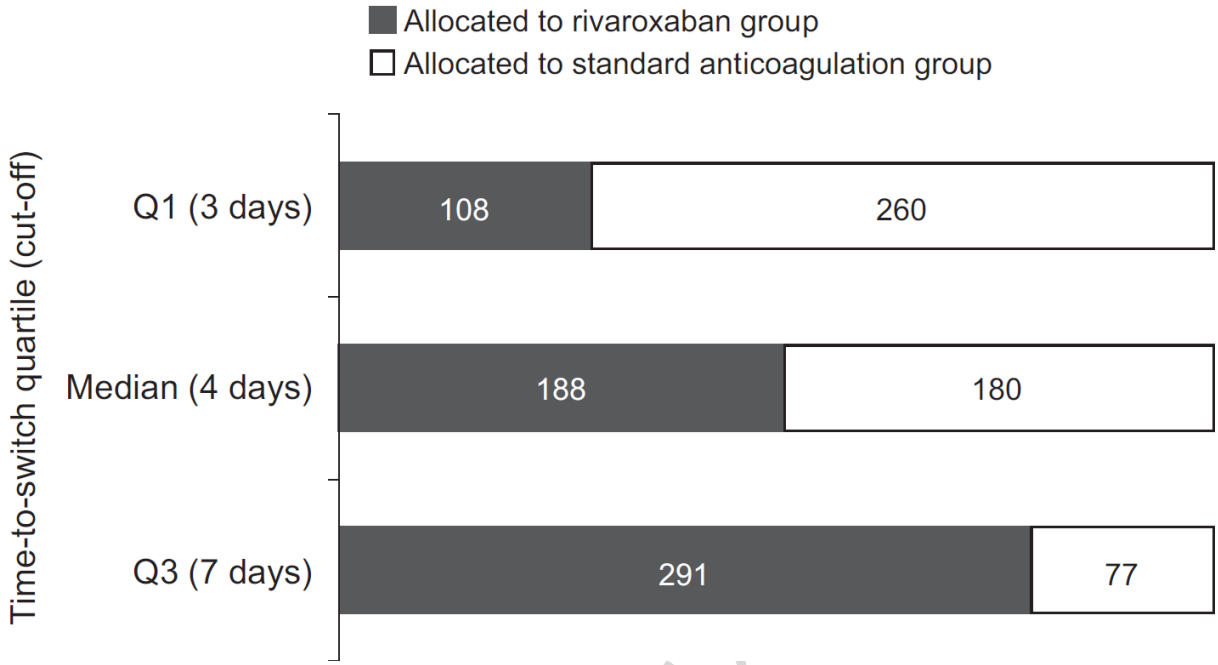

Figure 5