International Journal of Clinical Pharmacy (2019) 41:1625–1633
https://doi.org/10.1007/s11096-019-00928-x

RESEARCH ARTICLE

Patient adherence to rivaroxaban in deep vein thrombosis, a cohort study in Switzerland: quantitative results

Jennifer Dotta-Celio[1,2] · Adriano Alatri[3] · Isabella Locatelli[2] · Monique Salvi[3] · Olivier Bugnon[1,2] · Marie-Paule Schneider[1,2] · Lucia Mazzolai[3]

Received: 14 January 2019 / Accepted: 17 October 2019 / Published online: 28 November 2019

Abstract

Background Direct oral anticoagulants (DOACs) have the advantage of being administered orally at a fixed dose without laboratory monitoring, in contrast to the frequent international normalized ratio measurements used to adjust for vitamin K antagonists dosing. Rivaroxaban, has a short half-life. The anticoagulation effect rapidly decreases if medication adherence is suboptimal. *Objective* The purpose of this quantitative study (called RIVA) is to longitudinally describe adherence to rivaroxaban (implementation and persistence) in patients with deep vein thrombosis (DVT). *Setting* The community pharmacy of the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland in collaboration with the angiology division of the Lausanne University Hospital (CHUV). *Methods* This is an observational study. Patients received rivaroxaban for 3 or 6 months: 15 mg twice a day during the first 3 weeks and then 20 mg once a day until the end of the treatment. Adherence was measured using electronic monitoring. Implementation and adherence were modelled using a generalized estimating equation model. Persistence was represented using a Kaplan–Meier survival curve. *Main outcome measure* Medication adherence (implementation and persistence). *Results* Thirty-one consecutive patients were included (68% male, mean age: 47 years old). The collected adherence data consisted of 57 inter-visit phases, 2899 electronic monitoring openings and a median follow-up of 92 days (IQR: 87; 100). Implementation to rivaroxaban was initially high [96.3 (92.8; 98.1)] but decreased during the first 3 weeks, until it reached 89.3 (76.0; 95.6). After the switch from twice a day 15 mg to a once a day 20 mg regimen, implementation increased again and remained stable [95.4 (92.2; 97.3)] for 90 days. Four patients who experienced adverse events discontinued the treatment before the end of the study and were considered non-persistent (clinically appropriate discontinuation). *Conclusion* Adherence to rivaroxaban in deep vein thrombosis is high in persistent patients. Discontinuation is related to rivaroxaban adverse effects/toxicity. Implementation should be reinforced during the twice a day-phase, and this first 3-week experience should help patients and healthcare professionals choose the best timing for the once a day phase.

Keywords Anticoagulants · Electronic monitoring · Interprofessionality · Medication adherence · Rivaroxaban · Venous thrombosis

Impact of findings on practice statements

- Healthcare professionals (HPCs) should pay particular attention to the first phase of treatment with rivaroxiban (when taken 15 mg twice a day).
- HCPs should engage patients in choosing the best timing for rivaroxaban during the second phase of the treatment (once a day) according to their needs.
- Patients have to be informed on the possible occurrence of adverse effects and toxicity when initiating rivaroxa-

Jennifer Dotta-Celio and Adriano Alatri are equal first authors

Marie-Paule Schneider and Lucia Mazzolai are equal senior authors

All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

✉ Marie-Paule Schneider

Extended author information available on the last page of the article

ban, and have to be educated on how and when to inform HCPs.

Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Almost two-thirds of VTE cases are isolated deep vein thrombosis (i.e., without concomitant PE) [2]. In Europe, DVT has an annual incidence of approximately 70–140 cases/100,000 people [2].

For proximal DVT, anticoagulant therapy is recommended for 3 months if transient and reversible risk factors are present. In all other patients, the decision to discontinue anticoagulation should be individually tailored and balanced against bleeding risk, taking also into account patient preferences [2]. Direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) are used to treat DVT [2]. DOACs (rivaroxaban, apixaban, edoxaban, dabigatran) have the advantage of being administered orally at a fixed dose without laboratory monitoring, in contrast to the frequent international normalized ratio (INR) measurements used to adjust for VKAs dosing [3–5]. Systematic reviews and meta-analyses reported similar efficacy of DOACs compared to VKAs in the treatment of DVT and higher safety associated with a lower risk of bleeding [6–8].

Medication adherence is defined as the process by which patients take their medications as prescribed by their health care providers [9]. Medication adherence consists of three behavioural components: initiation, implementation and persistence. Initiation corresponds to whether or not the patient takes the first dose. Implementation is the correspondence between the doses taken by the patient and the prescribed doses (from the first dose until the last one) in terms of taking and timing. Persistence is the time between initiation and discontinuation [9].

Few studies have investigated adherence to DOACs or VKAs in DVT. No study evaluated initiation. A retrospective study evaluated the medication possession ratio (MPR) to rivaroxaban and warfarin in DVT [10]. Three studies evaluated discontinuation to rivaroxaban caused by adverse effects [11–13]. One study compared three different adherence tools (eCAP™, medication diaries, and pill count) to monitor rivaroxaban (n = 19) and apixaban (n = 20) [14].

However, no study explored the dynamic of drug intake over time through electronic monitoring. Rivaroxaban has a short half-life (5–9 h in adults and 11–13 h in elderly patients) and the anticoagulation effect rapidly decreases if medication adherence is suboptimal [15, 16].

Aim of the study

The purpose of the RIVA study was to explore adherence to rivaroxaban in patients with DVT. The study consisted of quantitative and qualitative substudies. The purpose of the quantitative substudy was to measure adherence to rivaroxaban (implementation and persistence) longitudinally. The qualitative study (individual interviews with patients) will be published separately; it aimed to explore the patients' perceptions and experiences of taking rivaroxaban.

Ethics approval

The study protocol was approved by the local ethic committee (Canton Vaud, Switzerland) in August 2014 (protocol 247/14). Informed consent was obtained from all individual participants included in the study.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Methods

The article has been written according to STROBE [17] and EMERGE [18] guidelines.

Study design and setting

The RIVA study is a single-group, monocentric, prospective, pilot study that took place between February 2015 and June 2017. The study was conducted at the community pharmacy of the Center for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland in collaboration with the angiology division of the Lausanne University Hospital (CHUV).

Participants

All consecutive outpatients (≥ 18 years) with a DVT of the lower limbs about to start rivaroxaban were eligible. Angiologists screened the patients during their medical visit. The choice to use DOAC instead of VKA was made on the basis of international and local guidelines and according to the patient's preferences. According to guidelines, DOAC should be considered the first choice in the treatment of DVT because they showed to have at least the same efficacy than VKA but less bleeding events. The only exceptions to use of DOAC are patients with severe renal failure (clearance

creatinine < 30 mL/min) and patients with severe obesity (patients weighted > 120 kg) [2]. Please note that at time when this study was designed rivaroxaban was the only DOAC available in Switzerland for DVT treatment. Patients' past medication adherence did not influence the choice of treatment.

The exclusion criteria were the patient's inability to understand and sign the informed consent form or to attend the study appointments. Since patients started rivaroxaban at the time of the study, previous medication adherence was not an eligibility criterion.

Patients were prescribed rivaroxaban for 3 or 6 months; 15 mg twice a day (BID) during the first 3 weeks and then 20 mg once a day (QD) until the end of the treatment. Patients were seen at the Angiology Division and at the pharmacy at V0 (baseline), V1 (3 weeks) and V2 (3 or 6 months depending on the duration of the treatment). If the patients needed to take rivaroxaban for 6 months, an additional visit at 3 months (V1b) was planned.

Variables and data sources

A case report form (CRF) was used at baseline to collect socio-demographic and medication data: age, gender, nationality, area of residence, ethnic group, current co-treatments, and the past or current use of an adherence aid.

At baseline, the angiologist filled in an anamnestic questionnaire to evaluate the venous thromboembolism risk factors (personal/familial history of VTE, obesity, cancer, thrombophilia, surgery, immobility), the cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, smoking), the history of cardiovascular disease and the presence of concomitant diseases.

Adherence to rivaroxaban was measured using an Electronic Monitoring system (EM, named MEMS®; Aardex Ltd.). This pillbox cap was equipped with an electronic chip that records the date and time of each opening. The use of the electronic pillbox made it possible to collect longitudinal data and to model the implementation and the persistence. Patients were asked to use the electronic pillbox as a regular pillbox and to open it only at the time of drug intake. The data recorded by the electronic chip were uploaded to computer software (MedAmigo®, Aardex Ltd.) at 3 weeks, 3 months and 6 months in a blinded manner. They were unblinded at the end of the study. Neither the researchers and healthcare professionals nor the patients had access to the results during the study.

Reconciliation of electronic adherence raw data with patient-reported EM use and pill count

To reduce the risk of bias associated with the adherence measure instrument, two reconciliation strategies were used: patient's reported EM use and a pill count. At each visit, patients were asked whether and in which circumstances they had prepared pocked doses (i.e., medication prepared in advance for a later use) and whether they encountered any nonmonitored period (NMP) (i.e., rivaroxaban taken without the electronic monitor, e.g., in case of hospitalization). At each visit (except for V1b), the remaining pills in the returned pillbox were stored at the pharmacy. At the end of the study, a manual pill count for each inter-visit period (also called patient-phase, time in days between two pharmacy visits, i.e., V0–V1, and V1 (V1b)–V2) was performed.

At the end of the study, electronic adherence data were extracted from the Medamigo® platform for each inter-visit period. A day was defined as the 24-h period from 3:00 a.m. to 2:59 a.m. on the next day because we considered a 2:00 a.m. drug intake as an evening and not a morning dose.

Then, the electronic adherence data were compared with pill counts for each patient-phase. The absolute difference between the electronic adherence (%EDM = electronic drug monitoring-based proportion of prescribed doses taken) and pill count (%PC = pill count-based proportion of prescribed doses taken) was calculated using the formula: ABS (%EDM − %PC) [19]. If this difference was > 25%, electronic adherence was recalculated by including pocked doses and nonmonitored periods reported by patients during the corresponding pharmacy visits (V1, V2).

Implementation, persistence and adherence definitions

Implementation is the time dependent percentage of patients taking correctly their medication among those who are still persistent at a given time. Persistence is the distribution of the individual times between initiation and discontinuation [9]. According to the definition, the discontinuation is "when the next dose to be taken is omitted and no more doses are taken thereafter" [9]. For this analysis, two definitions of discontinuation were considered: (1) "classic" ABC discontinuation (patient stops treatment on his own, unilateral initiative) [9] and (2) "classic" ABC discontinuation & clinically appropriate discontinuation (patient stops treatment according to medical pharmacovigilance recommendations, e.g., treatment adverse effects and toxicity). Patients who stopped using the electronic pillbox before the end of the study (e.g., a patient who decided to use a weekly box instead of the EM) but continued medication, and patients who had the medical visit some days before the end of the follow-up (e.g., at 86 days instead of 90 days) were considered as censored times [20]. Adherence summarizes implementation and persistence and is defined as the time dependent percentage of patients taking correctly their medication among patients initially included into the study.

Statistical methods

Descriptive statistics were used to analyse the demographic and clinical data: age, gender, weight, body mass index (BMI), VTE risk factors, cardiovascular risk factors, previous bleeding, acute coronary syndrome, and stroke.

Implementation and persistence were analysed over a period of 90 days, because only four patients provided data beyond this period. At each day, we dichotomized the patient medication behaviour in "correct" when he/she took at least the number of prescribed doses, and "incorrect" when he/she took less than the number of prescribed doses. Implementation was represented as a function of time and modelled using a generalized estimating equation (GEE) model. The exchangeable GEE model was chosen, and the time was introduced using polynoms. Times spent in the first phase (15 mg BID) and second phase (20 mg QD) were separately introduced in a piecewise GEE model also including a jump between the two phases [21].

Persistence was estimated using the Kaplan–Meier estimator. The latter is an estimator of the survival function of the discontinuation times taking into account censoring. Adherence was estimated at each day of the follow-up as the product between implementation and persistence (indirect estimation method) [20].

Results

Participants

Thirty-one patients were included. The planned duration of treatment was 3 months for 27 patients and 6 months for four patients. Twenty-one patients (67.7%) were male, and the mean age was 47 years old. Nine patients (29.0%) had a personal history of VTE, and nine patients (29.0%) a familial history of VTE. Sixteen patients (51.6%) were smokers (nine active and seven former smokers) (see Table 1).

Reconciliation of electronic monitor raw data with pill count

The collected adherence data for the 31 included patients consisted of 57 inter-visit phases, 2899 EM openings and a median follow-up of 92 days (IQR: 87; 100).

During the reconciliation process, the difference ABS(%EDM − PC) was > 25% in two patient-inter-visit phases. For one patient, the discrepancy was resolved by introducing a validated NMP. In a second patient-phase, pill count was unavailable, as the patient received the treatment in another pharmacy; the EM data were therefore reconciled with patient-reported EM use.

Table 1 Demographic and clinical characteristics of the 31 patients at baseline

Characteristics	
Age (years) (mean ± SD)	47.0 ± 13.5
Male sex (n, %)	21 (67.7%)
Weight (kg) (mean ± SD)	80.5 ± 16.0
BMI ≥ 30 (n, %)	8 (25.8%)
Venous thromboembolism risk factors	
Active cancer	1 (3.2%)
Central venous catheter	1 (3.2%)
Hospitalization < 1 month	4 (12.9%)
Surgery < 3 months	4 (12.9%)
Trauma < 1 month	5 (16.1%)
Immobilization < 1 month	3 (9.7%)
Bed rest ≥ 4 days (< 1 month)	5 (16.1%)
Oral contraception	4 (12.9%)
Long trip > 8 h, before the DVT	12 (38.7%)
Acute inflammatory disease	1 (3.2%)
Varicose veins	13 (41.9%)
Personal history of VTE	9 (29.0%) (five occurred post-surgery and four were idiopathic)
Familial history of VTE	9 (29.0%)
Inherited thrombophilia	0
Cardiovascular risk factors	
Arterial hypertension	3 (9.7%)
Dyslipidemia	2 (6.5%)
Diabetes	2 (6.5%)
Smoking	16 (51.6%)
Active smoking	9 (29.0%)
Former smoking	7 (22.6%)
Renal failure	0
Others	
Previous major bleeding[a]	2 (6.5%)
Acute coronary syndrome	0
Stroke	0

DVT deep vein thrombosis, *VTE* venous thromboembolism

[a]International Society on Thrombosis and Haemostasis (ISTH) major bleeding definitions in non-surgical patients: patients having symptomatic presentation and Fatal bleeding and/or Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells [22]

Implementation, persistence and adherence

Three individual patient behaviours are illustrated in Fig. 1: a patient with a perfect adherence and a regular timing (1a), a patient with a variable timing (1b) and a patient with a suboptimal adherence (1c).

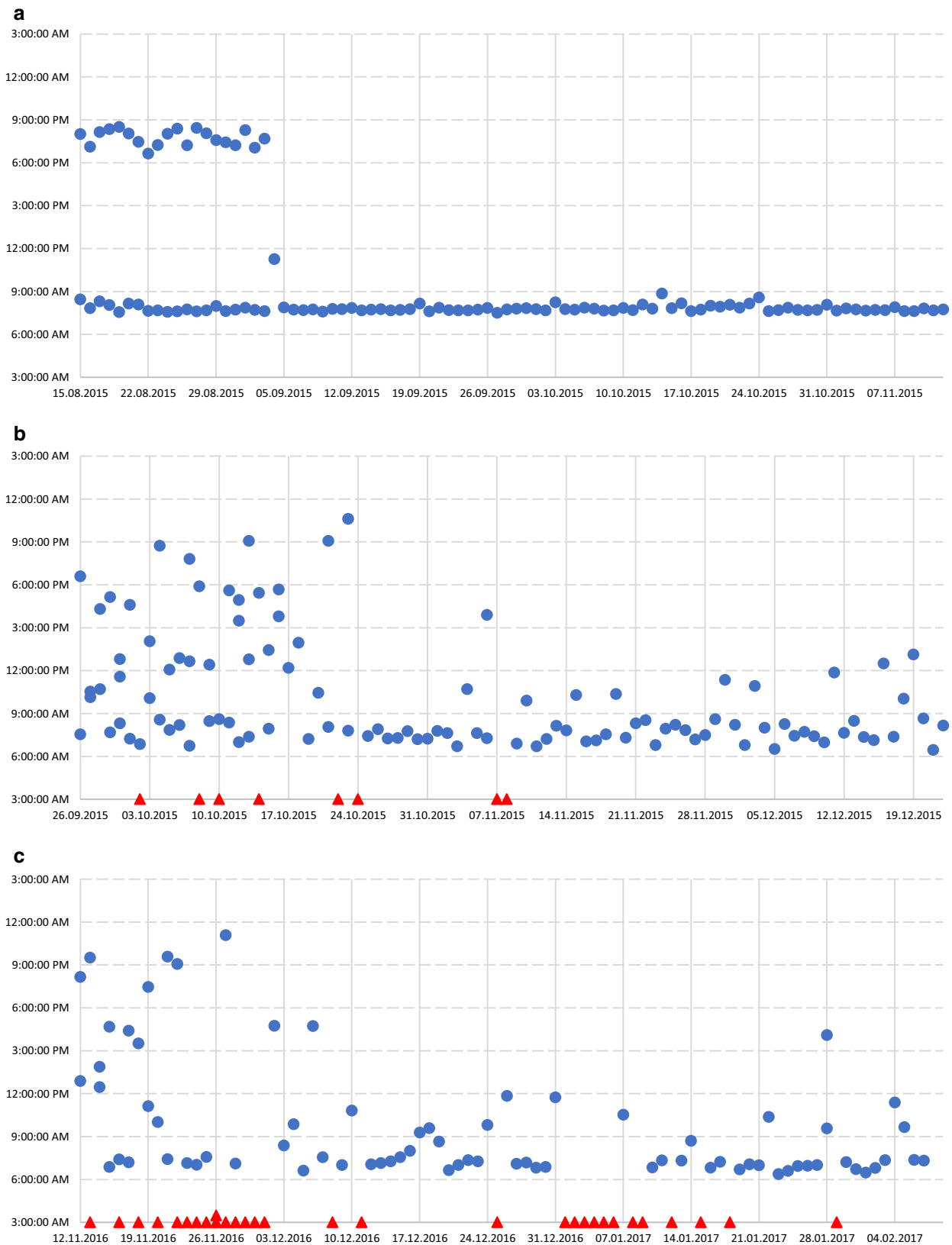

Fig. 1 Three individual medication implementation behaviors to rivaroxaban. The blue dots represent the date/time of all consecutive EM openings. The red triangles mark missed half-day or full-day EM openings. **a** A patient with a perfect adherence and a regular timing, **b** a patient with a variable timing resulting in missed doses, particularly during phase 1, **c** a patient with a suboptimal adherence

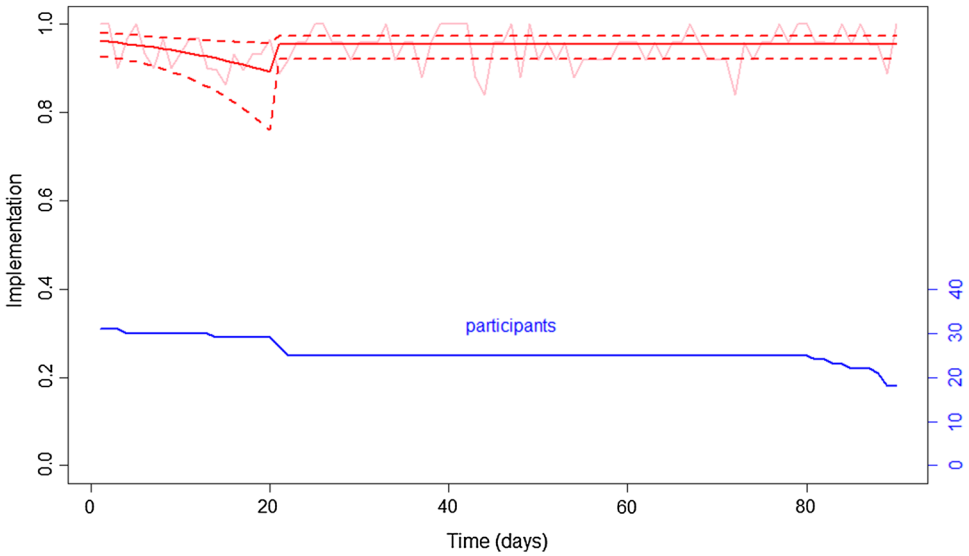

Fig. 2 Implementation results with the GEE exchangeable model. The pink curve represents the percentage of patients with correct number of daily opening(s) over time (implementation). Curves in red represent implementation prediction with 95% confidence interval for a subject changing regimen at 21 days, obtained via a piecewise GEE model including times spent in the first phase (15 mg BID) and in the second phase (20 mg QD) separately. Curve in blue represents the number of patients over time

Figure 2 shows implementation predicted by the model for a switch at 21 days, which represented the median switch time (range 20–24 days). A piecewise GEE model with the time variables (time in the first and the second phase) introduced using polynomes showed a significant implementation decrease during the first phase, from 96.3 (95% CI 92.8; 98.1) to 89.3 (95% CI 76.0; 95.6), followed by a significant jump at the beginning of the second phase, with a stabilization at 95.4 (95% CI 92.2; 97.3) until the end of monitoring.

Among the 31 patients, four were discontinuing for medical reasons (alveolar haemorrhage, gastrointestinal pain and nausea, uterine bleeding, or headache), all during the first 3-week phase of medication. No patient discontinued the treatment on one's own initiative. Two patients were censored at V1: one felt controlled and the other one preferred to use a weekly box instead of EM. Five patients had the medical visit some days before the end of follow-up (e.g., at 86 days instead of 90 days) and were censored at the day of the visit.

Figure 3 shows the persistence Kaplan–Meier estimate according to the second definition of discontinuation as an interruption of treatment on the patient's own initiative or according to medical recommendations. A 87% (75.8–99.7%) persistence was estimated at the end of the 3-month follow-up. Adherence estimated using the indirect method is also represented in the graph.

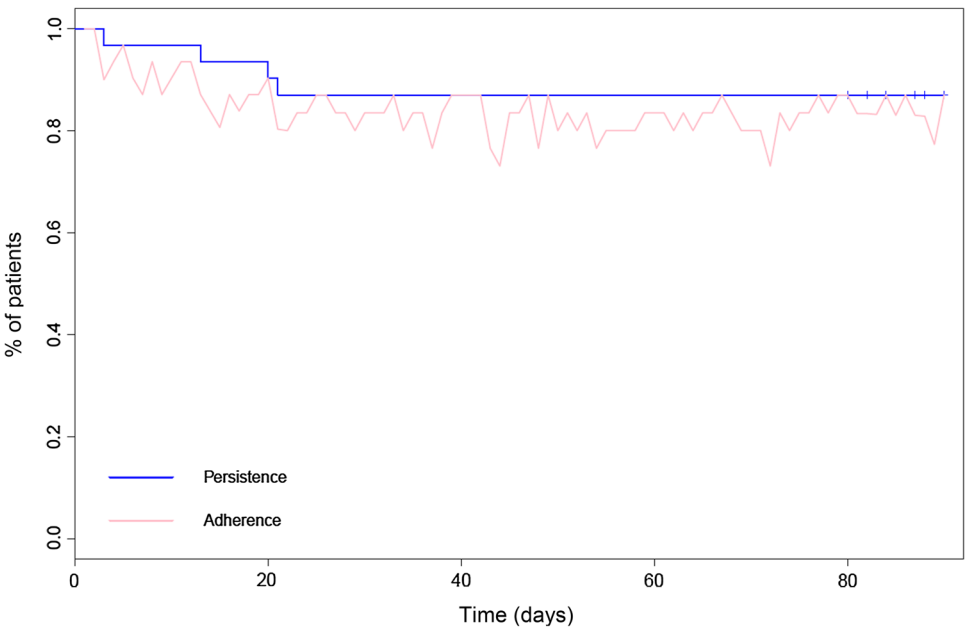

Fig. 3 Persistence and medication adherence. Curve in red represents adherence to rivaroxaban and curve in blue represents patient persistence to rivaroxaban

Discussion

The RIVA quantitative substudy described the 3-month adherence to rivaroxaban in patients with DVT of the lower limbs. The strength of the RIVA study relies on the electronic, longitudinal measure of medication adherence in a real-life context. The two behavioural constructs of adherence (implementation and persistence) were clearly defined and analysed individually. Advanced longitudinal statistical approaches were applied to describe the dynamics of adherence, firstly for the initial BID 3-week phase and, secondly, for the subsequent 9-week QD-phase.

Implementation measured in the RIVA study was in line with the results of other studies. In Lai et al.'s study ($n = 231$ patients, $n_{rivaroxaban} = 94$ patients), adherence to rivaroxaban was higher than adherence to warfarin (0.904 ± 0.094 vs. 0.804 ± 0.159), whatever the clinical indication. Adherence was calculated using the medication possession ratio (MPR), without specifying the adherence components (implementation and persistence) [10].

Interestingly, in the RIVA study, implementation of rivaroxaban BID decreased gradually during the first 3 weeks. We assume that this decrease was related to the fading of symptoms after the acute event passed. It has been established in different diseases that the disappearance of symptoms has a negative impact on medication adherence [23]. It is noteworthy that after the switch to the QD regimen, implementation of rivaroxaban improved again. This result corroborates other findings in the literature. A meta-analysis (29 studies using EM) confirmed that adherence to QD cardiovascular drugs is higher compared to BID (percent of days with correct dosing: 84.9% vs. 73.8%, $p < 0.01$) and three times daily regimens (65.4%, $p < 0.0001$) [24].

As described by Vrijens and Heidbuchel [16], missing a single dose of a DOAC BID regimen is not critical but missing a single dose in a QD regimen is equivalent to missing three consecutive doses of a BID regimen, hence reaching the ineffective drug concentration. On the other hand, according to patients' perspectives, QD regimens are easier to handle in daily life. What matters the most between the pharmacological and the patient perspectives? To better resolve this important dilemma, further studies are needed to evaluate the effect of the QD versus BID regimens on the factor Xa inhibition and on clinical outcomes. No study has yet investigated the association between adherence to rivaroxaban and its clinical outcomes in DVT. The RIVA study is paving the way by showing that the adherence behaviour varies largely from one patient to the next. Hence, healthcare professionals must consider the pharmacological aspects as well as the patients' adherence barriers and facilitators to convey the most appropriate and personalized health message, whether they are addressing adherence with an adherent or less adherent patient.

In the RIVA study, 4 patients (13%) had to interrupt the treatment (clinically appropriate discontinuation). In the XALIA study, 157 patients on rivaroxaban for DVT (out of 2619, 6%) experienced adverse events resulting in a drug discontinuation [12]. In the randomized Einstein-DVT Dose-Ranging study ($n = 543$), nine patients on rivaroxaban 20 mg (out of 135, 7%), 7 on rivaroxaban 30 mg (out of 134, 5%) and 5 on rivaroxaban 40 mg (out of 136, 4%) discontinued prematurely because of adverse events [11]. In the ongoing, prospective, non-interventional Dresden NOAC Registry, 3.6% of patients (out of 411) on rivaroxaban for acute lower limb DVT and/or PE had an unplanned, complete discontinuation (6.1% at 12 months) [13]. Informing patients of possible rivaroxaban adverse effects in the early stage of treatment is a priority for all health professionals.

The RIVA study has some limitations. First, the limited number of patients due to the pilot design. Despite the small number of patients, our preliminary results on implementation and persistence will help design larger studies. Second, patients who use an electronic pillbox tend to take their medication better during the first 4–5 weeks of follow-up, knowing they are being monitored [25]. Despite this limitation, we were able to show a decline in implementation to rivaroxaban during the first 3 weeks of treatment. EM allows the longitudinal description of adherence and the modelling of implementation and persistence as two complementary constructs [26]. Finally, it is assumed (but not ascertained) that patients swallow their treatment immediately after the EM opening. To control this limitation, patients were asked to open the pillbox only at the time of taking and to swallow the tablet immediately.

Conclusion

To our knowledge, the RIVA study is the first study that measures medication adherence in patients with DVT treated by rivaroxaban using an electronic monitoring system and exploiting longitudinal data. Medication adherence electronic monitoring should be used more systematically in daily practice to document suboptimal adherence. The health professionals could then provide solutions accordingly to patient needs. Importantly, implementation should be reinforced during BID phase one.

Finally, large, multicentre studies are needed to confirm these findings and to assess the impact of adherence to rivaroxaban on clinical outcomes and resolve the dilemma between the BID pharmacologically higher positive impact versus QD patient preference.

Acknowledgements The authors would like to acknowledge Aline Bourdin and Noura Bawab for their assistance with including patients. The authors would also like to thank the pharmacy team (and, in particular, the medication adherence program team) and the angiology team for their involvement in the study.

Funding None.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest Adriano Alatri is on an Advisory Board for Amgen, Bayer, and Pfizer. Lucia Mazzolai is on an Advisory Board for Bayer, Pfizer, and Sankyo. Jennifer Dotta-Celio, Isabella Locatelli, Monique Salvi, Olivier Bugnon, Marie Paule Schneider have no conflict of interest.

References

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464–74.
2. Mazzolai L, Aboyans V, Ageno W, Agnelli G, Alatri A, Bauersachs R, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European society of cardiology working groups of aorta and peripheral circulation and pulmonary circulation and right ventricular function. Eur Heart J. 2018;39:4208–18.
3. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood. 2010;115(1):15–20.
4. Amin A, Marrs JC. Direct oral anticoagulants for the management of thromboembolic disorders: the importance of adherence and persistence in achieving beneficial outcomes. Clin Appl Thromb Hemost. 2016;22(7):605–16.
5. Hanemaaijer S, Sodihardjo F, Horikx A, Wensing M, De Smet PA, Bouvy ML, et al. Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands. Int J Clin Pharm. 2015;37(6):1128–35.
6. Cohen AT, Hamilton M, Mitchell SA, Phatak H, Liu X, Bird A, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. PLoS ONE. 2015;10(12):e0144856.
7. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320–8.
8. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA. 2014;312(11):1122–35.
9. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
10. Lai YF, Neo JK, Cheen MH, Kong MC, Tai BC, Ng HJ. Comparison of medication adherence and treatment persistence between new oral anticoagulant and warfarin among patients. Ann Acad Med Singap. 2016;45(1):12–7.
11. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, 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. 2008;112(6):2242–7.
12. Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, 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. 2016;3(1):e12–21.
13. Keller L, Marten S, Hecker J, Sahin K, Tittl L, Beyer-Westendorf J. Venous thromboembolism therapy with rivaroxaban in daily-care patients: results from the Dresden NOAC registry. Int J Cardiol. 2018;257:276–82.
14. Castellucci LA, Chiang P, Pecarskie A, Le Gal G, Rodger M. Comparing medication adherence tools for the direct oral anticoagulants rivaroxaban and apixaban. Blood. 2017;130(Suppl 1):3713.
15. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53(1):1–16.
16. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace. 2015;17(4):514–23.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7.
18. De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, et al. ESPACOMP medication adherence reporting guideline (EMERGE). Ann Intern Med. 2018;169(1):30–5.
19. Rotzinger A, Cavassini M, Bugnon O, Schneider MP. Development of an algorithm for analysing the electronic measurement of medication adherence in routine HIV care. Int J Clin Pharm. 2016;38(5):1210–8.
20. Schneider MP, Achtari Jeanneret L, Chevaux B, Backes C, Wagner AD, Bugnon O, et al. A novel approach to better characterize medication adherence in oral anticancer treatments. Front Pharmacol. 2018;9:1567.
21. Gertsch A, Michel O, Locatelli I, Bugnon O, Rickenbach M, Cavassini M, et al. Adherence to antiretroviral treatment decreases during postpartum compared to pregnancy: a longitudinal electronic monitoring study. AIDS Patient Care STDS. 2013;27(4):208–10.
22. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692–4.
23. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol. 2013;4:91.
24. Coleman CI, Roberts MS, Sobieraj DM, Lee S, Alam T, Kaur R. Effect of dosing frequency on chronic cardiovascular disease medication adherence. Curr Med Res Opin. 2012;28(5):669–80.
25. Cook P, Schmiege S, McClean M, Aagaard L, Kahook M. Practical and analytic issues in the electronic assessment of adherence. West J Nurs Res. 2012;34(5):598–620.
26. Lehmann A, Aslani P, Ahmed R, Celio J, Gauchet A, Bedouch P, et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014;36(1):55–69.

Affiliations

Jennifer Dotta-Celio[1,2] · Adriano Alatri[3] · Isabella Locatelli[2] · Monique Salvi[3] · Olivier Bugnon[1,2] · Marie-Paule Schneider[1,2] · Lucia Mazzolai[3]

Jennifer Dotta-Celio
jennifer.celio@unisante.ch

[1] Community Pharmacy, Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland

[2] Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

[3] Angiology Division, Heart and Vessel Department, Lausanne University Hospital, Lausanne, Switzerland