Thrombosis Research 163 (2018) 6–11

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Rivaroxaban versus warfarin for the prevention of post-thrombotic syndrome

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ARTICLE INFO

Keywords:
Deep vein thrombosis
Post-thrombotic syndrome
Quality of life
Rivaroxaban
Warfarin

ABSTRACT

Introduction: Despite treatment of acute deep vein thrombosis (DVT) with low molecular weight heparin and warfarin, up to 50% of patients develop post-thrombotic syndrome (PTS). Our aims were to assess whether treatment of DVT with rivaroxaban would reduce the rate of subsequent PTS and improve health-related quality of life (HRQoL) as compared to conventional anticoagulation with low molecular weight heparin (LMWH)/warfarin.

Materials and methods: Consecutive patients with an objectively confirmed DVT diagnosed between 2011 and 2014 and treated with either rivaroxaban or warfarin were included in this study 24 (± 6) months after DVT. PTS was assessed using the Patient Reported Villalta scale. HRQoL was assessed using the EQ-5D-3L and VEINES-QOL/Sym questionnaires.

Results: Total 309 patients were included, 161 (52%) treated with rivaroxaban and 148 (48%) with warfarin. Rivaroxaban-treated patients had a lower rate of PTS (45%: 95% confidence interval [CI] 37 to 52) compared to those treated with warfarin (59%: 95% CI 51 to 66, absolute risk difference 14%: 95% CI 3 to 25, odds ratio (OR) 0.6, P = .01). The adjusted OR for development of PTS was 0.5 (95% CI: 0.3 to 0.8, P = .01) in patients treated with rivaroxaban. HRQoL was significantly better in the rivaroxaban-treated patients. HRQoL measured by EQ-VAS (P = .002) and VEINES-QOL/Sym (P = .005/P = .003) remained significantly better after adjustment.

Conclusions: Patients treated with rivaroxaban had lower rate of PTS and better HRQoL after DVT compared to patients treated with warfarin. However, these results should be interpreted with caution due to the limitation imposed by study design.

1. Introduction

Despite properly applied anticoagulation with initial subcutaneous injections of low molecular weight heparin (LMWH) followed by long-term treatment with oral vitamin K antagonist (VKA) for the treatment of acute deep vein thrombosis (DVT) of the lower extremities, up to 50% of patients develop post-thrombotic syndrome (PTS) [1, 2]. PTS is characterized by varying grades of chronic manifestations including pain, heaviness, swelling, itching, skin pigmentation and, at worst, chronic ulceration of the leg [3]. PTS negatively affects health-related quality of life (HRQoL) [4, 5] and imposes a significant economic burden on healthcare systems [2, 6].

Since no specific or curative treatment of PTS is currently available, prevention is essential. The type of initial treatment and the quality of anticoagulation have been shown to affect the prevalence of PTS [7, 8]. Patients with suboptimal international normalized ratio (INR) values > 50% of the time in the first 3 months of treatment were are at higher risk of developing PTS [7]. Treatment with tinzaparin has been shown to be associated with a lower rate of PTS as compared to patients who received standard care with warfarin for ≥12 weeks at home [9]. Pooled analyses of randomized controlled trials (RCT) that compared extended LMWH with warfarin reported a lower rate of PTS and venous ulcers in patients treated with LMWH only [10]. Based on these reports, it has been postulated that rapid and stable anticoagulation may minimize the clot burden and thus reduce the risk of PTS [11].

Recently, early thrombus removal by catheter-directed thrombolytic therapy in addition to conventional treatment with LMWH and warfarin was shown to be associated with a 15% absolute reduction in the rate of

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https://doi.org/10.1016/j.thromres.2018.01.013
Received 1 November 2017; Received in revised form 17 December 2017; Accepted 7 January 2018
Available online 08 January 2018
0049-3848/

PTS after two years as compared to conventional treatment alone demonstrating the importance of early clot removal [12], although this result was not confirmed in another RCT [13].

Direct-acting oral anticoagulants (DOAC), also termed non-vitamin K acting oral anticoagulants, lack many of the limitations inherent of VKAs, such as the need for regular monitoring, fluctuation of effect, and the many interactions with food and other drugs [14]. There is now a large body of evidence demonstrating the efficacy and safety of DOACs in the treatment of venous thromboembolism (VTE). Based on this evidence, the 2016 updated American College of Chest Physicians (ACCP) guidelines suggest the use of DOACs as first-line treatment of DVT [15]. These agents include the direct thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban. In phase 3 studies, all four agents showed non-inferiority to treatment with LMWH/warfarin for the prevention of recurrent VTE [16–19]. Because of the short time to peak effect and possibly more stable anticoagulation effect over time, a question of whether DOACs can reduce the risk of PTS has been raised [11, 20].

In the present study, we aimed to determine whether treatment of DVT with rivaroxaban would reduce the rate of subsequent PTS as compared to conventional anticoagulation with LMWH/warfarin. Knowing that PTS is an important predictor of reduced HRQoL, we also aimed to assess whether treatment with rivaroxaban would improve HRQoL after DVT.

2. Materials and methods

2.1. Study population

Patients with a diagnosis of acute DVT of a lower extremity between 2011 and 2014 were identified from three Norwegian hospitals (Østfold Hospital, Kalnes, Akershus University Hospital, Lorenskog, and Oslo University Hospital, Ullevål) by searching the respective hospital databases for ICD-10 codes of DVT (I80.1, I80.2, and I80.3) or through a local hospital registry (Thrombosis Registry of Østfold Hospital – The TROLL registry).

Inclusion criteria were age ≥18 years, objectively confirmed first time ipsilateral DVT in a lower limb by compression ultrasonography or venography, and patients who had received at least 90 days of anticoagulation either with initial LMWH and warfarin or rivaroxaban.

Exclusion criteria included presence of previous DVT in the ipsilateral extremity, extended use of LMWH alone prior to the initiation of oral anticoagulant defined by > 10 of the first 90 treatment days (patients treated with concomitant warfarin and LMWH were not excluded if LMWH was received for > 10 days), and unwillingness or inability to provide informed consent.

2.2. Study design, conduct and endpoints

The study was designed as a cross-sectional study where patients with first time ipsilateral DVT who had received anticoagulation therapy with either warfarin or rivaroxaban were evaluated for PTS and HRQoL 24 (± 6) months after DVT, to determine whether treatment with rivaroxaban would result in a lower rate of PTS and improved HRQoL as compared to treatment with warfarin. Patients were assigned to a particular group if they had received either rivaroxaban or warfarin for at least 80 of the first 90 days of treatment.

All eligible patients who were alive were invited by letter. After agreeing to participate, informed consent and study forms for evaluation of PTS and HRQoL were sent to participants by post. Patients were asked to complete and return the forms prior to the study visit where patients were interviewed and examined to collect clinical information. Those who were not able or unwilling to attend a consultation (n = 87) were interviewed by telephone to collect and verify clinical data.

The primary outcome measure was PTS assessed by the Patient Reported Villalta scale [21]. The secondary outcome measure was HRQoL assessed by the EQ-5D-3L- [22, 23] and the Venous Insufficiency Epidemiological and Economic Study (VEINES)-QOL/Sym questionnaires [24, 25].

Collected clinical data included: information on localization of DVT, type of and duration of anticoagulation, recurrent DVT(s), comorbidities, body mass index (BMI), sociodemographic data, and presence of provoking factors, Provoking factors were defined transient triggering factors occurring < 3 months prior to the index event (orthopedic surgery, other extensive surgery, trauma or hospitalization with immobilization, long-haul flight for over 4 h or childbirth) [26]. Patients with active cancer or chemotherapy six months prior to diagnosis are generally treated with LMWH and were excluded from the study.

Comorbidities were determined by reviewing the patients' hospital medical records as well as by reviewing ICD-10 diagnosis codes for hospital admissions and ambulatory visits for the last 10 years prior to and up until study inclusion to compute the Charlson Comorbidity Index (CCI), which was expressed as a continuous variable [27].

The study was conducted according to the principles founded in the revised declaration of Helsinki. Consent was acquired from participating patients. The study was approved by the Norwegian South Eastern Regional Committee for Medical and Health Research Ethics, REK nr.2013/1253, and was registered at ClinicalTrials.gov with unique identifier no NCT02268630 with acronym LOVE (Long-term Outcome after Venous thromboEmbolism) study.

2.3. Assessment of outcomes

2.3.1. Post-thrombotic syndrome

PTS was assessed only once at 24 (± 6) after DVT and at least three months after a recurrent DVT, using the Patient Reported Villalta scale, which is a visually assisted form for patients' reporting of signs and symptoms of the Villalta scale [21]. The form includes a comprehensive explanatory text in Norwegian of all 11 elements of the Villalta scale and their grading, and records presence or absence of venous ulceration. A score of > four points in a lower limb with previous DVT was defined as PTS [21]. The severity of PTS was classified according to the PRV score into mild [5–9], moderate (10–14 points), or severe (≥15 points or venous ulceration).

2.3.2. HRQoL questionnaires

EQ-5D is a standardized instrument to assess generic HRQoL [22, 23]. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). These health states can be converted into a single index value, using one of the available EQ-5D value sets. The value sets have been derived using VAS or time-trade-off valuation techniques, and reflect the opinion of the general population. EQ-5D index value scores assign each health state a value ranging from −0.59 to 1.00, where 1.00 indicates perfect health and 0.00 indicates death. The instrument includes the EQ Visual Analogue Scale (EQ VAS), scored from zero indicating “worst imaginable health state” to 100 indicating “best imaginable health state” [28, 29].

VEINES-QOL/Sym is a disease-specific HRQoL instrument for patients with chronic venous disease. The questionnaire consists of 26 items regarding leg problems. Items regarding limitations in daily activities and psychological impact during the previous four weeks are included, and two summary scores are computed; VEINES-QOL and VEINES-Sym [24, 25]. For both scores, higher scores indicate better outcomes.

2.4. Statistical analysis

Based on existing literature, we hypothesized that treatment with rivaroxaban would be associated with a 13% reduction in the rate of PTS at two years as compared to warfarin [9, 30]. With a type one statistical error of < 5% and a type two statistical error of < 20%, a sample size of 370 patients was estimated.