

RIVAROXABAN VERSUS DABIGATRAN: A NEW ERA IN VENOUS THROMBOEMBOLISM TREATMENT

RIVAROKSABAN NASPRAM DABIGATRANA: NOVA ERA U TRETMANU VENSKEG TROMBOEMBOLIZMA

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Summary

Considering the frequency of deep vein thrombosis and pulmonary embolism, the therapy of these two conditions takes an important place in vascular surgery. Among numerous therapeutic options, new oral anticoagulants, such as rivaroxaban or dabigatran, represent a great improvement in the treatment of venous thromboembolism.

Searching MEDLINE base until December 1, 2015 using MESH term "Rivaroxaban versus Dabigatran in VTE", we found 7 studies investigating the usage of new oral anticoagulants in venous thromboembolism treatment. The total of 18,841 patients was enrolled. No head-to-head studies were found.

Benefits such as lower therapy price, oral use and greater comfort for patients and health providers place new oral anticoagulants to the frontline of venous thromboembolism treatment.

However, we need head to-head studies to have a clear picture of these two drugs.

Keywords: Rivaroxaban, Dabigatran, new oral anticoagulants, venous thromboembolism, deep vein thrombosis, pulmonary embolism.

Sažetak

Uzimajući u obzir incidenciju tromboze dubokih vena i plućne embolije, terapija ovih stanja zauzima značajno mesto u vaskularnoj hirurgiji. Postoji više izbora lečenja, a novi oralni antikoagulansi, kao što su rivaroksaban i dabigatran, predstavljaju veliki pomak u terapiji venskih tromboembolijskih stanja.

Pretražujući bazu podataka MEDLINE koristeći MESH izraz "Rivaroxaban versus Dabigatran in VTE" pronađeno je 7 studija sa ukupno 18841 ispitanikom. Nije pronađena nijedna studija koja direktno upoređuje upotrebu rivaroksabana i dabigatrana u terapiji venskih tromboembolijskih stanja.

Oralna upotreba, niža cena lečenja kao i veći komfor za pacijente i lekare prednosti su novih oralnih antikoagulanasa u terapiji venskih tromboembolijskih stanja.

Studije koje direktno upoređuju Rivaroxaban i Dabigatran su neophodne radi boljeg razumevanja efekata ova dva leka.

Ključne reči: Rivaroksaban, Dabigatran, novi oralni antikoagulansi, venski tromboembolizam, dubinska venska tromboza, embolija pluća

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE) are not that rare in vascular pathology. DVT occurs in 1 per 1000 adults each year, increasing to 7 per 1000 yearly in population aged ≥ 75 (1-3). Incidence of PE amounts to 49 per 100,000 persons (4). It is an expensive condition to treat, costing between \$7.5 to \$39 billion per year in the USA alone (5). Postthrombotic syndrome (PTS), which occurs in 20-60% of patients with prior DVT, increases the cost of treatment up to 75% (6). A study of Tagalakis et al. evaluated short and long-term mortality after 67,354 definite and 35,123 probable cases of VTE. They found that 30-day and one year case fatality rates were 10.6 and 23.0%, respectively (7).

In recent years, several new oral anticoagulants (NOACs) have been developed for the treatment of VTE, such as direct factor Xa inhibitor rivaroxaban (Xarelto®, Bayer AG, Leverkusen, Germany) (8) and direct thrombin

inhibitor dabigatran (Pradaxa®, Boehringer Ingelheim, Ingelheim, Germany) (9). Dabigatran has just recently been approved for treating acute VTE and it was approved for prevention of recurrent events in early 2014. Rivaroxaban was approved for this indication by the Food and Drug Administration (FDA) in 2012 (10).

NOACs have opened a new chapter in VTE treatment, aiming at succeeding vitamin K antagonists (VKA). Comparison of NOACs and warfarin are shown in Table 1 (11, 12).

This review aims at summarizing the literature and previous studies of rivaroxaban and dabigatran in the treatment of VTE.

Table 1. Pharmacological characteristics of Rivaroxaban and Dabigatran in comparison with Warfarin

	Rivaroxaban	Dabigatran	Warfarin
Mechanism of action	Direct factor Xa inhibition	Direct thrombin inhibition	Inhibition of vitamin K epoxide-reductase
Molecular weight (Da)	436	628	≈ 1000
Bioavailability	80-100% with food	6-7%	>60%
Half-life	7-13 h	9-17 h	36-42 h
Dosing	Fixed, once daily	Fixed, once-twice daily	INR adjusted variable dosing
Protein binding (%)	92-95	33-35	≈99
Elimination	67% renal (half as an inactive form)	80% renal	Hepatic, primarily via CYP2C9
Reversal strategy	None	None	Vitamin K
Monitoring test	Not required routinely. Anti-Xa assay, PT with Neoplastin	Not required routinely. Diluted thrombin time	INR

Abbreviations: CYP, cytochrome P450; INR, international normalized ratio; PT – prothrombin time; Xa, activated Factor X.

METHODS

We pre-specified the objectives and methods of this systematic review. Key points of interest were studies that compared the usage of rivaroxaban and dabigatran in treating acute and chronic DVT and PE. Studies were identified by scanning reference lists of other review articles and by searching MEDLINE base using PUBMED until December 1, 2015. We used MESH term “Rivaroxaban versus Dabigatran in VTE”. Only full – text articles were included.

RESULTS

The results of our search included 7 studies: 4 studies in acute VTE and 3 studies in chronic VTE treatment. Four studies investigated the usage of dabigatran (2 studies in acute and 2 studies in chronic VTE) while the usage of rivaroxaban was shown in 3 studies (2 studies in acute and one study in chronic VTE treatment). No head-to-head studies were found. 18,841 patients in total were enrolled. Across trials 55 – 61% of patients were males, the average age was 55 - 58 (11) (Table 2).

All the trials were double blinded, except EINSTEIN-DVT and EINSTEIN-PE. The assessment methods of recurrent VTE were consistent across studies (13-17). DVT diagnosis was established by venography or compression ultrasonography (CUS) of leg veins. Non-fatal PE was diagnosed using ventilation-perfusion lung scanning, angiography or spiral computed tomography of pulmonary arteries. Diagnosis of fatal PE was based on autopsy findings or death for which PE could not be excluded.

Bleeding definition criteria differed between trials (18, 19). Major bleeding was defined as symptomatic (dabigatran trials) or overt (rivaroxaban trials). Episodes of bleeding that did not match major bleeding criteria, but still needed medical observation, were defined as clini-

cally relevant non-major (CRNM) bleeding. RECOVER I and II trials defined CRNM bleeding as one requiring hospitalization and/or surgery, and transfusion of <2 U of whole blood or red blood cells (10).

Trials with dabigatran considered the presence of symptomatic proximal DVT (defined as occurring in popliteal vein and above) with or without PE. Patients included in RE-MEDY or RE-SONATE trials had completed at least 3 months of treatment with warfarin or dabigatran (10). EINSTEIN PE trial included patients with symptomatic PE, with/without DVT, while EINSTEIN DVT trial required symptomatic proximal DVT without PE. EINSTEIN-Extension trial evaluated the long-term use of rivaroxaban for secondary prevention of VTE. Only EINSTEIN trials allowed concomitant use of dual antiplatelet therapy.

Exclusion criteria were similar across the studies: life expectancy < 3 months (EINSTEIN DVT, -PE) or < 6 months (RE-COVER I, II); creatinine clearance (CrCl) ≤ 30 mL/min and pregnancy as well.

Heparin lead-in was used in RE-COVER, while in EINSTEIN trials experimental group was taking only rivaroxaban. Treatment durations ranged from 3 to 12 months in acute VTE treatment and 6 to 18 months in the extended therapy of VTE.

Placebo controlled studies were superiority trials (NOACs had better outcome than placebo), while other studies used non-inferiority approach (NOACs weren't inferior to drugs used in control groups). In trials with placebo-controlled groups patients were recruited if there was clinical doubt of continuation or cessation of anticoagulant therapy.

Table 2. Clinical trials with NOACs in VTE treatment

Study (NOAC)	N (patients)	Age (yrs)	Male sex (%)	Design	Experimental treatment	Control treatment
Acute treatment						
RE-COVER I ^[13] (Dabigatran)	2,564	55	58	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
RE-COVER II ^[14] (Dabigatran)	2,589	55	61	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
EINSTEIN DVT ^[15] (Rivaroxaban)	3,449	56	57	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
EINSTEIN PE ^[16] (Rivaroxaban)	4,833	58	53	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
Extended treatment						
RE-MEDY ^[17] (Dabigatran)	2,866	55	61	DBRCNI	DAB 150 mg BID	Warfarin dose-adjusted (INR: 2.0–3.0)
RE-SONATE ^[17] (Dabigatran)	1,343	56	55	DBRCS	DAB 150 mg BID	Placebo
EINSTEIN-EXTENSION ^[15] (Rivaroxaban)	1,197	58	58	DBRCS	RIV 20 mg OD	Placebo

Abbreviations: BID, twice-daily; DAB, dabigatran; DBRCNI, double-blind randomized controlled non-inferiority trial; DBRCS, double-blind randomized controlled superiority trial; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; INR, International Normalized Ratio; N, total patients in the trial; NOAC, new oral anticoagulant; OD, once-daily; OLRCNI, open-label randomized controlled non-inferiority trial; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etexilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; RIV, rivaroxaban; VTE, venous thromboembolism; yrs, years.

DISCUSSION

Acute VTE treatment trials showed no difference in recurrent, symptomatic VTE between two groups. In the active-control RE-MEDY trial, dabigatran demonstrated non-inferiority compared with warfarin regarding to recurrence of VTE (10). RE-SONATE trial, showed a 92 % reduction in the recurrent VTE, representing superiority of dabigatran over placebo (10). The incidence of recurrent, symptomatic VTE in EINSTEIN EXT trial was reduced by 82 % with the use of rivaroxaban (15). Death incidence related to VTE didn't differ significantly between trials (10, 15).

Bleeding complications were considerably reduced with the use of dabigatran in RE-COVER trials, as well as in RE-MEDY trial. While incidence of major bleeding was not notably increased with the use of dabigatran in RE-SONATE trial, there was a significant increase of other bleeding complications (10).

EINSTEIN-PE study showed reduced incidence of major bleeding in patients taking rivaroxaban. There was no difference of bleeding complications between groups

in EINSTEIN-DVT trial. While the incidence of major bleeding in EINSTEIN-EXT trial showed no difference between groups, there was a significant increase of major or CRNM bleeding with the use of rivaroxaban. This increase was mainly presented as haematuria (9 vs 0), epistaxis (8 vs 1), and rectal bleeding (7 vs 2 events) (15).

Because of different CRNM bleeding definitions across trials, there was a wide variation in event rates, such as 3.8% incidence in RE-COVER II and a much higher incidence of 9.5% in EINSTEIN-PE. Major and CRNM bleeding were significantly reduced in those receiving dabigatran, but not rivaroxaban when compared with standard of care (10).

According to the data collected in the study investigating the use of NOACs in thromboprophylaxis after joint-replacement surgery (20), risk difference (RD) between the two drugs indicates a small and insignificant benefit in favour of rivaroxaban. At the same time, RD regarding major or CRNM bleeding indicates a difference that disfavours direct factor Xa inhibitor and which, although of borderline significance, indicates a true difference between treatments in this study (20).

Apart from bleeding complications, dyspepsia was the major side effect of dabigatran (10, 12). Proton pump inhibitors, used to treat dyspepsia, reduce absorption of dabigatran for 30% (11). Dabigatran doesn't have to be taken with food; on the other side, taking rivaroxaban without food decreases its absorption by 39% (11), which may lead to subtherapeutic plasma concentrations. Since NOACs have shorter half-life (<24h) than OACs (36-42h), suboptimal adherence of rivaroxaban or dabigatran may be more dangerous. Advanced liver disease is a contraindication to rivaroxaban use (21).

Renal elimination is higher in dabigatran comparing to rivaroxaban; therefore, using direct thrombin inhibitor is contraindicated in severe renal insufficiency (CrCl < 30mL/min) while taking direct factor Xa inhibitor is not recommended if CrCl < 15mL/min (11). Dose adjustment might be needed in some cases. Due to differences in renal excretion, hemodialysis can be used to treat overdosing with dabigatran, eliminating 50-60% of circulating dosage, which cannot be applied to rivaroxaban (9). Administration of activated charcoal may be useful to reduce absorption of rivaroxaban if taken less than six hours after overdose or accidental ingestion (8).

If bleeding continues or is life threatening, procoagulants, such as factor VIIa or prothrombin complex concentrates (activated or inactivated) can be administered, although the evidence of their effectiveness is limited (22). Highly specific antidotes for factor Xa and direct thrombin inhibitors are under development and might be available during upcoming years (23).

Furthermore, twice-daily dosing schedule of dabigatran might be more difficult for some patients to adhere to a daily regimen in contrary to rivaroxaban, which is used once daily. A dose adjustment needed at day 21 with the use of rivaroxaban requires communication between healthcare provider and patient during transition period. Dabigatran does not require any dose alteration in the first weeks of therapy and may provide a simpler approach after patient discharge. However, lead-in with parenteral anticoagulant therapy in case of dabigatran can be uncomfortable for some patients.

Perhaps the most interesting difference between Xarelto® and Pradaxa® is the incidence of arterial thrombosis. Whereas the rivaroxaban seems to be superior to other anticoagulants, the dabigatran elevates the risk of arterial thrombosis (24). Rivaroxaban also decreases the risk of myocardial infarction relative to warfarin (25) whereas dabigatran slightly increases this risk (26). The differences suggest that factor Xa inhibition may be more effective than thrombin inhibition in arterial circulation.

As low molecular weight drugs, rivaroxaban and dabigatran pass through placental barrier and therefore are contraindicated to be used in pregnancy (22). In women with child bearing potential, NOACs must be prescribed with contraceptive pills and used with caution.

Elderly population deserves brief discussion. The incidence of VTE rises exponentially in older adults (6). Older patients are also more likely to have various comorbidities, such as cancer, renal impairment, higher risk of bleeding or they use P-glycoprotein (P-gp) or CYP3A4 inducers/inhibitors. Therapy with NOACs in elderly patients with DVT and PE should be done carefully. As the average age of patients in conducted studies ranged from 55 to 58 years, efficacy and safety of rivaroxaban and dabigatran use in this group remain unclear.

CONCLUSION

VTE takes an important place in vascular surgery, with significant morbidity and mortality rates. It also represents an expensive condition to treat. By evidences based on literature and trials investigating clinical use of rivaroxaban and dabigatran, none of them seemed dominant over the other. Benefits such as lower therapy price, oral use and greater comfort for patients and healthcare providers place NOACs to frontline of VTE treatment. We need head-to-head studies to have more clear picture of these two drugs; until then, clinicians will be forced to make treatment decisions based on their own experience.

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