Research Review™
STUDY REVIEW

Rivaroxaban versus enoxaparin/vitamin K antagonist therapy in patients with venous thromboembolism and renal impairment

Making Education Easy 2022

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Abbreviations used in this review:

AF = atrial fibrillation
CAD = coronary artery disease
CrCl = creatinine clearance
DVT = deep vein thrombosis
INR = international normalised ratio
PAD = peripheral artery disease
PE = pulmonary embolism
VKA = vitamin K antagonist
VTE = venous thromboembolism

Publication overview

This review summarises the results of the pre-specified subgroup analysis of the EINSTEIN DVT and EINSTEIN PE studies. These studies examined the efficacy and safety of oral rivaroxaban in patients with venous thromboembolism (VTE) with and without renal impairment by comparing fixed-dose rivaroxaban with enoxaparin and an international normalised ratio (INR) titrated vitamin K antagonist (VKA).[1] Both studies were open-label, randomised, event-driven, non-inferiority trials that compared oral rivaroxaban alone with subcutaneous enoxaparin followed by a VKA in patients with acute, symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PE).[1] Patients were categorised into four groups based on renal function (normal renal function and mild, moderate, and severe renal impairment) for the analysis. Rivaroxaban was found to show similar efficacy as standard-therapy and was associated with a significantly lower rate of major bleeding. The key patient subgroups demonstrated consistent efficacy and safety results. The study showed that renal impairment to any degree increased the risk of major bleeding in enoxaparin/VKA-treated patients compared to rivaroxaban-treated patients.

Rivaroxaban is a highly selective direct Factor Xa inhibitor that functions as an antithrombotic agent.[2] As a Factor Xa inhibitor, rivaroxaban prevents conversion of prothrombin to thrombin through the prothrombinase complex, ultimately preventing fibrin clot formation and activation of platelets by thrombin.[2] In Australia, rivaroxaban (XARELTO®) is indicated for the prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs, prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) as well as for the prevention of recurrent DVT and PE.[2] It is also indicated, in combination with aspirin, for the prevention of major cardiovascular events in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD).[2]

Study Background

Patients with symptomatic venous thromboembolism (VTE) and renal impairment are at increased risk of recurrent VTE, both DVT and PE, and are also at increased risk of bleeding if they receive classical anticoagulation for VTE.[1] Rivaroxaban, like other direct oral anticoagulants, is renally excreted. Reduced renal clearance with increasing renal impairment, results in increased plasma exposure and pharmacodynamic effects that could be associated with an increased bleeding risk.[3] Consequently, it is important to understand the effect of renal impairment on the efficacy and safety of rivaroxaban in VTE patients to minimise the risk of bleeding while ensuring optimal anticoagulation in patients with renal impairment.[1]

Expert comment

Many patients who require anticoagulation for venous thrombosis will have varying degrees of renal impairment. As such, insight in to the safety and efficacy of rivaroxaban in this subgroup is paramount. Moreover, there can be a tendency to believe that non-renally cleared drugs, such as warfarin, will be safer in patients with renal impairment, where in fact the opposite is the case. This study highlights the superior safety of rivaroxaban in patients with renal impairment.

Study Design and Methods

Both the EINSTEIN DVT and EINSTEIN PE studies were open-label, randomised, event-driven, non-inferiority studies that compared oral rivaroxaban alone with subcutaneous enoxaparin followed by a VKA in patients with acute, symptomatic DVT and/or PE.

EINSTEIN DVT STUDY[4]

In 3449 patients with acute, symptomatic DVT, oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. The primary efficacy outcome was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant non-major bleeding.

EINSTEIN PE STUDY[5]

In 4832 patients with acute symptomatic pulmonary embolism with or without deep-vein thrombosis, rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared with standard therapy with enoxaparin followed by an adjusted-dose VKA for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant non-major bleeding.

Endpoints and Analyses

As an event-driven study, the endpoints were recurrent VTE and major or clinically relevant non-major bleeding in patients.

Study Results

Patient Characteristics

In total, 4150 patients were assigned to rivaroxaban and 4131 were assigned to enoxaparin/VKA.

The median age of patients in the rivaroxaban group was 58.0 years and in the enoxaparin/VKA group was 59.0 years (**Table 1**). There were more male (n = 4516) than female (n = 3765) patients in the study.

The renal function status, sex distribution and mean age of the patients were as follows:

Renal Function Status	n (%)	% Female	Mean Age (Years)
Normal Renal Function (≥80 ml/min)	5569 (67.3%)	40.5%	49.9
Mild Renal Impairment (50-79 ml/min)	2037 (24.6%)	52.7%	69.6
Moderate Renal Impairment (30-49 ml/min)	636 (7.7%)	65.9%	78.2
Severe Renal Impairment (<30 ml/min)	21 (0.3%)	76.2%	76.8

The main demographic characteristics within the subgroups were similar for rivaroxaban and enoxaparin/VKA (**Table 1**).

Table 1. Demographic characteristics of EINSTEIN DVT and EINSTEIN PE patients combined[1]

	Rivaroxaban n=4150	Enoxaperin/VKA n=4131
Age, median (Q1-Q3), y	58.0 (45.0–71.0)	59.0 (45.0–70.0)
Female sex, n (%)	1848 (44.5)	1917 (46.4)
Weight, median (Q1-Q3), kg	80.0 (70.0–93.0)	80.0 (70.0–93.0)
Creatinine clearance		
≥80 ml/min, n (%)	2772 (66.8)	2797 (67.7)
Age, median (Q1-Q3), y	50.0 (39.0–61.0)	51.0 (40.0–61.0)
Female sex, n (%)	1113 (40.2)	1140 (40.8)
Weight, median (Q1-Q3), kg	85.0 (74.0–98.0)	85.0 (75.0–98.0)
50-79 ml/min, n (%)	1036 (25.0)	1001 (24.2)
Age, median (Q1-Q3), y	71.0 (64.0–77.0)	71.0 (65.0–77.0)
Female sex, n (%)	520 (50.2)	553 (55.2)
Weight, median (Q1-Q3), kg	74.8 (65.0–82.0)	74.0 (65.0–82.0)
30-49 ml/min, n (%)	323 (7.8)	313 (7.6)
Age, median (Q1-Q3), y	80.0 (75.0–84.0)	79.0 (75.0–83.0)
Female sex, n (%)	209 (64.7)	210 (67.1)
Weight, median (Q1-Q3), kg	67.0 (59.0–75.1)	67.8 (59.0–75.0)
<30 ml/min, n (%)	10 (0.2)	11 (0.3)
Age, median (Q1-Q3), y	80.5 (73.0–86.0)	79.9 (77.0–86.0)
Female sex, n (%)	5 (50.0)	11 (100.0)
Weight, median (Q1-Q3), kg	60.0 (50.0–68.0)	70.0 (48.0–75.0)
Missing, n (%)	9 (0.2)	9 (0.2)
Risk factors for VTE		
Unprovoked VTE, n (%)	2003 (48.3)	2048 (49.6)
Previous VTE, n (%)	791 (19.1)	819 (19.8)
Active cancer, n (%)	232 (5.6)	198 (4.8)

Q = quartile; **VKA** = vitamin K antagonist; **VTE** = venous thromboembolism.

Recurrent VTE

In previous studies, rivaroxaban was found to be non-inferior to enoxaparin/VKA for the prevention of recurrent VTE.[6, 7]

In this analysis, the rates of recurrent VTE for both treatments combined were 1.8%, 2.8%, 3.3%, and 4.8% in patients with normal renal function and mild, moderate, and severe renal impairment, respectively. The respective incidence rates for rivaroxaban and enoxaparin/VKA patients are shown in **Figure 1** and **Table 2**.

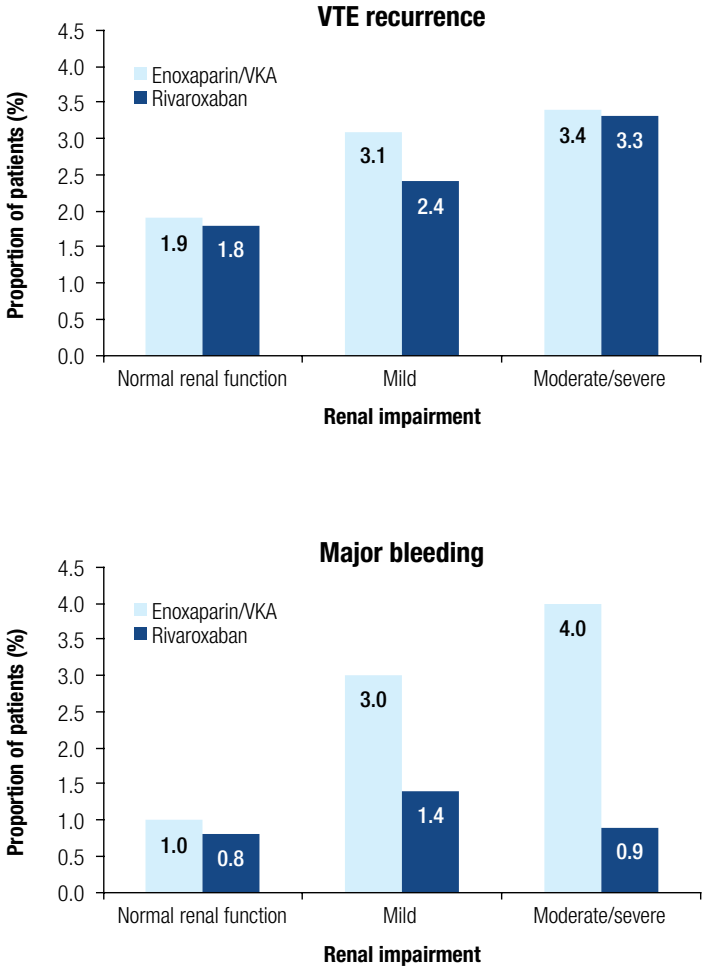

Figure 1. Recurrent VTE and bleeding in relation to renal function across the entire analysis period.[1] EINSTEIN DVT and EINSTEIN PE patients. **VKA** = vitamin K antagonist; **VTE** = venous thromboembolism.

Bleeding and Renal Function

In a pooled analysis of both studies, a first clinically relevant non-major or major bleeding event occurred in 388 patients (9.4%) in the rivaroxaban group and in 412 patients (10.0%) in the enoxaparin/VKA group.[6]

In patients who received rivaroxaban, major and clinically relevant non-major bleeding occurred in 8.7% of patients with normal renal function, in 10.7% of those with mild renal impairment, in 11.6% of those with moderate renal impairment, and in 22.2% of those with severe renal impairment. In patients who received enoxaparin/VKA, these incidences were 8.8%, 12.3%, 13.9%, and 9.1%, respectively (**Table 2**).

Major bleeding occurred in 40 (1.0%) rivaroxaban and 72 (1.7%) enoxaparin/VKA recipients (HR 0.54; 95% CI 0.37–0.79; p = 0.002; **Table 3**). In patients receiving rivaroxaban, major bleeding occurred in 0.8% of patients with normal renal function, in 1.4% of those with mild renal impairment, in 0.9% of those with moderate renal impairment, and in 0% of those with severe renal impairment. In the enoxaparin/VKA group, these incidences were 1.0%, 3.0%, 3.9%, and 9.1%, respectively (**Table 2**). Notably, the risk of major bleeding was significantly increased in renally impaired patients treated with enoxaparin/VKA, whereas renal impairment across all stages did not increase major bleeding rates in patients treated with rivaroxaban.

Table 2. Recurrent VTE and bleeding in relation to renal function, treatment, and treatment period: EINSTEIN DVT and EINSTEIN PE patients combined*[1]

	Entire analysis period		Period up to 14 days		Period after 14 days	
	Rivaroxaban n=4150	Enoxaparin/VKA n=4131	Rivaroxaban n=4150	Enoxaparin/VKA n=4131	Rivaroxaban n=4054	Enoxaparin/VKA n=4001
Recurrent VTE n/N (%)						
Total of recurrent VTE	86	95	38	37	48	58
Normal renal function	50/2772 (1.8)	52/2797 (1.9)	23/2772 (0.8)	26/2797 (0.9)	27/2720 (1.0)	26/2716 (1.0)
Mild renal impairment	25/1036 (2.4)	31/1001 (3.1)	10/1036 (1.0)	8/1001 (0.8)	15/1009 (1.5)	23/974 (2.4)
Moderate renal impairment	11/323 (3.4)	10/313 (3.2)	5/3.23 (1.5)	2/313 (0.6)	6/307 (2.0)	8/296 (2.7)
Severe renal impairment	0/10 (0)	1/11 (9.1)	0/10 (0)	1/11 (9.1)	0/10 (0)	0/8 (0)
Missing	0/9 (0)	1/9 (11.1)	0/9 (0)	0/9 (0)	0/8 (0)	1/7 (14.3)
Major bleeding n/N (%)						
Total of major bleeding events	40	72	13	27	27	45
Normal renal function	23/2763 (0.8)	29/2786 (1.0)	8/2763 (0.3)	11/2786 (0.4)	15/2689 (0.6)	18/2704 (0.7)
Mild renal impairment	14/1030 (1.4)	30/1002 (3.0)	5/1030 (0.5)	10/1002 (1.0)	9/985 (0.9)	20/954 (2.1)
Moderate renal impairment	3/320 (0.9)	12/310 (3.9)	0/320 (0)	5/310 (1.6)	3/305 (1.0)	7/285 (2.5)
Severe renal impairment	0/9 (0)	1/11 (9.1)	0/9 (0)	1/11 (9.1)	0/9 (0)	0/6 (0)
Missing	0/8 (0)	0/7 (0)	0/8 (0)	0/7 (0)	0/8 (0)	0/7 (0)
Major and clinically relevant nonmajor bleeding n/N (%)						
Total of major and clinically relevant nonmajor bleeding events	388	412	129	134	259	278
Normal renal function	239/2763 (8.7)	245/2786 (8.8)	75/2763 (2.7)	73/2786 (2.6)	164/2627 (6.2)	172/2646 (6.5)
Mild renal impairment	110/1030 (10.7)	123/1002 (12.3)	40/1030 (3.9)	40/1002 (4.0)	70/957 (7.3)	83/927 (9.0)
Moderate renal impairment	37/320 (11.6)	43/310 (13.9)	14/320 (4.4)	20/310 (6.5)	23/291 (7.9)	23/272 (8.5)
Severe renal impairment	2/9 (22.2)	1/11 (9.1)	0/9 (0)	1/11 (9.1)	2/9 (22.2)	0/6 (0)
Missing	0/8 (0)	0/7 (0)	0/8 (0)	0/7 (0)	0/8 (0)	0/7 (0)

VKA = vitamin K antagonist; **VTE** = venous thromboembolism.
*Outcomes do not include censored patients or patients who had an event before Day 14.

Table 3. Presentation of major bleeding for rivaroxaban and enoxaparin/VKA patients separately[1]

	Rivaroxaban n=4130	Enoxaparain/VKA n=4116
First major bleeding, n (%)		
Any	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Retroperitoneal	0	1 (<0.1)
Intracranial	2 (<0.1)	4 (0.1)
Gastrointestinal	1 (<0.1)	2 (<0.1)
Thorax	0	1 (<0.1)
Nonfatal bleeding in critical site	10 (0.2)	27 (0.7)
Retroperitoneal	1 (<0.1)	7 (0.2)
Intracranial	3 (<0.1)	9 (0.2)
Intraocular	3 (<0.1)	3 (<0.1)
Pericardial	0	2 (<0.1)
Intra-articular	0	4 (0.1)
Adrenal	1 (<0.1)	0
Pulmonary	1 (<0.1)	0
Abdominal	1 (<0.1)	2 (<0.1)
Nonfatal, noncritical site bleeding but associated with a fall in haemoglobin ≥2 g/dl and/or transfusions ≥2 units	27 (0.7)	37 (0.9)
Surgical site	0	3 (<0.1)
Skin	1 (<0.1)	5 (0.1)
Urogenital	9 (0.2)	3 (<0.1)*
Gastrointestinal	14 (0.3)	24 (0.6)
Nasal	1 (<0.1)	0
Pulmonary	1 (<0.1)	0
Intramuscular	1 (<0.1)	2 (<0.1)

VKA = vitamin K antagonist.
*One patient had a combined gastrointestinal/urogenital bleeding event; this event is counted as gastrointestinal only.

Expert comment

Rivaroxaban is at least as efficacious as enoxaparin/warfarin in the acute treatment of both DVT and PE.

Apart from efficacy and ease of dosing, the low major and clinically relevant non-major bleeding rates, have meant that rivaroxaban has become one of the direct oral anticoagulants that represents the new standard of care in the treatment of VTE.

Renal impairment increases event rates, both for recurrent VTE and bleeding, in general. As the direct oral anticoagulants are renally excreted there can be a feeling that warfarin is a safer option in patients with renal impairment. This is not that case, and like with the AF data, the magnitude of benefit amplifies in favour of rivaroxaban as renal impairment worsens.

Put bluntly, it is much safer to use rivaroxaban in patients with renal impairment than warfarin.

It is fair to note however, that by the nature of the trial design, there were few patients with severe renal failure for analysis.

Study Interpretation

As previously demonstrated in other studies, this analysis of the data accumulated in the EINSTEIN DVT and EINSTEIN PE studies indicated that the risks of recurrent VTE and bleeding increase with declining renal function. The results also demonstrated that a dosage of rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily, had similar efficacy compared with standard treatment across patients with normal renal function or mild-to-moderate renal impairment.

The combined outcome of major or clinically relevant non-major bleeding showed numerically lower incidences with rivaroxaban compared with enoxaparin/VKA. There was a significant and clinically important reduction in major bleeding with rivaroxaban compared with enoxaparin/VKA, particularly in patients with mild or moderate renal impairment

In patients presenting with symptomatic VTE and mild-to-moderate renal impairment, large phase III trials have provided support that rivaroxaban can be administered at a fixed dose without adjustment for renal function and carries a safety advantage compared with standard treatment with enoxaparin/VKA, while maintaining efficacy.

For patients with a long-term indication for anticoagulation, the use of rivaroxaban may offer a broad safety window for patients with declining renal function that is not covered by the regular monitoring of renal function, which is usually recommended. A limitation of this analysis is that severe renal impairment, defined as CrCl <30 ml/min, was an exclusion criterion, and while few of these patients were randomised, little evidence is available for this group. Also, the data collection did not account for significant changes in patients' renal function over the course of treatment. Rivaroxaban is not recommended in patients with CrCl <15 ml/min, and it should be used with caution in patients with CrCl 15–29 ml/min.

The authors concluded that both recurrent venous thromboembolic complications and the risk of bleeding increase with declining kidney function in patients with symptomatic DVT or PE. The standard regimen of rivaroxaban, given without a dose reduction, is efficacious and associated with a lower incidence of major bleeding compared with treatment with enoxaparin/VKA.

Take home messages

- Patients with symptomatic venous thromboembolism (VTE) and renal impairment are at increased risk of recurrent VTE.
- Renally impaired patients treated with classical anticoagulation for venous thromboembolism (VTE) are at increased risk of bleeding and possibly pulmonary embolism.
- This analysis showed that renal impairment increased the risk of major bleeding in enoxaparin/VKA-treated patients but not in rivaroxaban-treated patients.
- Results from this analysis indicate that there is no requirement for rivaroxaban dose reduction due to renal impairment in patients being treated for acute VTE.

Expert concluding remarks

In patients with renal impairment rivaroxaban, without dose adjustment, remains a standard of care for the treatment of acute VTE.

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