

ORIGINAL ARTICLE



Rivaroxaban and Apixaban for Initial Treatment of Acute Venous Thromboembolism of Atypical Location

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Background

- Approximately 4% of venous thrombotic events are defined as “venous thromboembolism of atypical location” (VTE-AL) because involve alternate venous segments such as splanchnic, renal, gonadal, and cerebral territories.
- VTE-AL often reflect the pathology of the organ drained and are commonly associated with malignancy.
- There is no clinical data supporting the use of rivaroxaban and apixaban for the treatment of VTE-AL.
- The aim of the present study was to assess the efficacy and safety of rivaroxaban and apixaban in patients with acute VTE-AL.

Methods

- Prospective study.
- Consecutive patients enrolled into the Mayo Thrombophilia Clinic Registry between March 1, 2013, and February 1, 2017.
- Three groups of patients: VTE-AL treated with DOACs, VTE-AL treated with enoxaparin, typical VTE (VTE-TL) treated with DOACs.
- The primary efficacy outcome was venous or arterial thromboembolism.
- The primary safety end point was major bleeding.
- The secondary safety end point was clinically relevant non-major bleeding and the composite of major bleeding and clinically relevant non-major bleeding.

Results (1)

- 623 patients with acute VTE including 63 with VTE-AL
- Within the VTE-AL group, there were 36 patients receiving DOACs: rivaroxaban (n 22) or apixaban (n 14), whereas 23 were treated with enoxaparin and 4 with warfarin.
- There were 52.8% patients with underlying malignancy within the VTE-AL group receiving DOAC compared with 95.7% patients with malignancy treated with enoxaparin (P<.001).
- Patients with VTE-AL treated with a DOAC were younger compared with patients with VTE-TL.

TABLE 1. Demographic Characteristics of Patients With Acute Venous Thromboembolism (VTE) of Atypical Location (VTE-AL) or Typical Location (VTE-TL) Treated With Direct Oral Anticoagulant (DOAC: rivaroxaban or apixaban), or With Enoxaparin^{a,b}

Variable	VTE-AL DOAC (N=36 ^c)	VTE-TL DOAC (N=352 ^d)	P value	VTE-AL enoxaparin (N=23)	VTE-AL DOAC vs enoxaparin P value
Age (y), mean ± SD	53.6±14.1	61.1±14.1	.002	59.8±11.3	.08
Sex: female	23 (63.9)	152 (43.7)	.021	6 (26.1)	.005
Presence of PE	3 (8.3)	131 (37.2)	<.001	0 (0.0)	.15
BMI, mean ± SD	28.8±5.6	30.1±6.7	.27	26.8±4.0	.13
CrCl <50 mL/min	3 (8.3)	35 (9.9)	.76	3 (13.0)	.56
Malignancy	19 (52.8)	166 (47.2)	.52	22 (95.7)	<.001
Chemotherapy	13 (36.1)	112 (31.8)	.60	12 (52.2)	.22
Recent ^e surgery	11 (30.6)	74 (21.0)	.19	6 (26.1)	.72
Thrombophilia	0 (0.0)	14 (4.0)	.22	0 (0.0)	NA
Hormonal therapy	1 (2.8)	12 (3.4)	.84	0 (0.0)	.42
Previous VTE	5 (14.3)	67 (20.4)	.39	3 (15.0)	.94
Time from diagnosis to study drug initiation			.16		.12
Median	1	0		0	
Q1, Q3	0.0, 4.5	0.0, 2.0		0.0, 1.0	

^aBMI = body mass index; CrCl = creatinine clearance; NA = not applicable/available; PE = pulmonary embolism; Q1 = quarter 1; Q3 = quarter 3.

^bValues represent n (%) unless otherwise indicated.

^cRivaroxaban (n=22), apixaban (n=14).

^dRivaroxaban (n=219) or apixaban (n=133).

^eRecent indicates within the last 30 d.

Results (2)

- No differences between the three groups of patients regarding primary efficacy and safety endpoints.
- Restricting the analysis to cancer patients only, VTE recurrence rates were significantly higher in patients with VTE-AL treated with DOAC compared with patients with VTE-TL but not different from patients with VTE-AL treated with enoxaparin.
- Mortality rates were higher in patients with VTE-AL treated with a DOAC when compared with patients with VTE-TL but not different to those with VTE-AL treated with enoxaparin.
- Only patients with cancer died during the study period.

TABLE 3. Clinical Outcome in Patients With Acute Venous Thromboembolism (VTE) of Atypical Location (VTE-AL). With VTE of Typical Location (VTE-TL) Treated With Direct Oral Anticoagulants (DOACs): Rivaroxaban and Apixaban and in Patients With VTE-AL Treated With Enoxaparin

Outcome rate per 100 person-years	VTE-AL DOAC (n=36)	VTE-TL DOAC (n=352)	P value	VTE-AL enoxaparin (n=23)	VTE-AL DOAC vs enoxaparin P value
Overall					
VTE Recurrence (n)	2	7	.13	3	.26
Total follow-up person-years	27.4	298.3		12.7	
Recurrence rate (95% CI)	7.3 (0.88-26.3)	2.4 (0.94-4.8)		23.7 (4.9-69.1)	
Major bleed (n)	2	9	.26	3	.31
Total follow-up person-years	27.6	301.9		13.4	
Major bleed rate (95% CI)	7.2 (0.88-26.1)	3.0 (1.4-5.7)		22.4 (4.6-65.4)	
CRNM bleeding (n)	1	25	.38	2	.19
Total follow-up person-years	27.6	287.6		12.8	
Minor bleed rate (95% CI)	3.6 (0.1-20.2)	8.7 (5.6-12.8)		15.6 (1.9-56.3)	
Major or CRNM bleeding (n)	3	33	.95	5	.12
Total follow-up person-years	27.3	287.2		12.7	
Major or minor rate (95% CI)	11.0 (2.3-32.2)	11.5 (7.9-16.1)		39.4 (12.8-91.9)	
Death (n)	6	25	.03	5	.51
Total follow-up person-years	28.0	302.6		13.5	
Death rate (95% CI)	21.5 (7.9-46.7)	8.3 (5.3-12.2)		36.9 (12.0-86.1)	
Patients with cancer only					
VTE Recurrence (n)	2	4	.002	3	.81
Total follow-up person-years	7.9	151.9		12.3	
Recurrence rate (95% CI)	25.4 (3.1-91.8)	2.6 (0.72-6.7)		24.4 (5.0-71.4)	
Major bleed (n)	2	8	.22	3	.76
Total follow-up person-years	8.1	154.3		13.0	
Major bleed rate (95% CI)	24.8 (3.0-89.5)	5.2 (2.2-10.2)		23.1 (4.8-67.4)	
CRNM bleeding (n)	1	17	.72	2	.58
Total follow-up person-years	8.1	147.40		12.42	
Minor bleed rate (95% CI)	12.4 (0.31-69.2)	11.5 (6.7-18.5)		16.1 (2.0-58.1)	
Major or CRNM bleeding (n)	3	24	.55	5	.62
Total follow-up person-years	7.7	146.9		12.3	
Major or minor rate (95% CI)	38.9 (8.0-113.7)	16.3 (10.5-24.3)		40.7 (13.2-95.0)	
Death (n)	6	25	.001	5	.26
Total follow-up person-years	8.4	155.0		13.1	
Death rate (95% CI)	71.4 (26.2-155.3)	16.1 (10.4-23.8)		38.1 (12.- 88.8)	

CRNM = clinically relevant nonmajor.

Discussion

- This is the first prospective study to assess the efficacy and safety of rivaroxaban and apixaban in patients with venous thrombosis occurring in atypical locations.
- The VTE recurrence and major bleeding rates were similar when compared with patients with VTE in typical location.
- Outcomes were also similar compared with patients with atypical VTE treated with enoxaparin.
- Mortality rates in VTE-AL patients treated with rivaroxaban and apixaban were higher compared with patients with VTE-TL but not different than in patients with VTE-AL treated with enoxaparin.

Conclusions

- In summary, the results of this study indicate that rivaroxaban and apixaban use in patients with atypical venous thrombosis is associated with comparable efficacy and safety as in patients with typical VTE and similar to enoxaparin.
- The present study results may not be generalized to other DOACs.