Renal function and clinical outcome of patients with cancer-associated venous thromboembolism randomized to receive apixaban or dalteparin. Results from the Caravaggio trial

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Supplementary data

Inclusion and exclusion criteria

Any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known intra-cerebral metastases and acute leukemia) that met at least one of the following criteria were included: i) active cancer defined as a diagnosis of cancer within six months before the study inclusion, or treatment for cancer at the time of inclusion or during 6 months before randomization, or recurrent locally advanced or metastatic cancer; ii) cancer diagnosed within 2 years before the study inclusion (history of cancer).

Main exclusion criteria included: i) Eastern Cooperative Oncology Group (ECOG) Performance Status III or IV or life expectancy of less than 6 months; ii) administration of therapeutic doses of LMWH, fondaparinux, or unfractionated heparin for more than 72 hours or three or more doses of vitamin K antagonist before randomization; iii) active or high risk of bleeding contraindicating anticoagulant treatment or concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy; iv) hemoglobin level lower than 8 g/dL or platelet count < 75x109/L or history of heparin-induced thrombocytopenia or liver failure.

Randomization was centrally performed through an interactive online system and stratified according to the type of VTE (symptomatic or incidental) and timing of the cancer diagnosis (active or history of cancer). Patients underwent scheduled visits at four weeks, three, six and seven months after randomization, and anytime during the study if required by intervening clinical events.

Definition of study outcome events

The primary outcome was objectively confirmed recurrent VTE, which included proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal) occurring during the 6-month trial period.

The principal safety outcome of the Caravaggio study was major bleeding defined as acute clinically overt bleeding associated with one or more of the following: a decrease in the hemoglobin level of at least two grams per deciliter, a transfusion of two or more units of red cells, bleeding occurring at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome,

or retroperitoneal), bleeding resulting in surgical intervention, or fatal bleeding. Secondary safety outcomes included: clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major; clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding.

Renal function assessment

Creatinine was locally measured at the study centers, mainly by the use of calibrated enzymatic assays. All available assessments of renal function (starting from study treatment initiation) and on study outcome events were collected at each visit and anytime during the study period if necessary. Phone contact was planned for those patients not returning for follow-up visit at seven months from inclusion in Caravaggio. eGFR was calculated using three accepted methods (Cockcroft-Gault; Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); Modification of Diet in Renal Disease (MDRD) as follows:

- Cockcroft-Gault: eGFR = {[(140-age) x weight in Kg]/(72 x serum creatinine)} x (0·85 if female); [1]
- CKD-EPI: eGFR = 141 x min (serum creatinine / k)$^{\alpha}$ x max (serum creatinine / k)$^{-1.209}$ x $0{\cdot}993^{age}$ x (1·018 if female) x (1·159 if black). [2]

  In this equation, k is 0·7 for females and 0·9 for males; α is -0·329 for females and -0·411 for males; min indicates the minimum of (serum creatinine / k) or 1; max indicates the maximum of (serum creatinine / k) or 1; the equation does not require weight as the results are reported normalized to 1·73 m^2 body surface area, which is an accepted average adult surface area.
- MDRD: eGFR = 186 x (serum creatinine) $^{-1.154}$ x (age) $^{-0.203}$ x (0·742 if female) x (1·210 if black). [3]

Statistical analysis

Patients included in the Caravaggio study who received at least one dose of study treatment (modified intention to treat population) were included in this analysis. Study patients were censored at the time of death or permanent discontinuation or 180 days from randomization. Patients who experienced non-major bleeding remained in the study unless anticoagulant treatment was permanently discontinued. Differences in patient characteristics between the apixaban and dalteparin groups, between patients with vs. without study outcome events, and between patients with eGFR above and below predefined cut off

values were analyzed with descriptive statistics. Values were presented as mean ± SD or median, respectively.

To assess the effect of RI in the risk for study outcome events, two different analyses were performed:

i.) comparison of event rates in subgroups of patients randomized to apixaban or dalteparin identified based on a specific cut-off level for eGFR (60 or 50 ml per minute) at inclusion in the study;

ii.) proportional hazards model for the time to study outcome events with eGFR (according to the Cockroft-Gault formula) as a time-varying covariate. In these analyses, missing values in eGFR post-baseline measurements were replaced using LOCF method.

Cumulative incidences were presented either as proportion or per patient-year.

Appendix Table 1. Baseline characteristics of the study population

	All patients N= 1142 (%)
Age mean ± SD	67·7 ± 11·1
> 75 years, *n (%)*	296 (25·9)
Range	21 - 93
Female gender, *n*	579
BMI, mean ± SD	26·7 ± 5·2
Locally advanced or metastatic cancer, *n (%)*	779 (68·2)
ECOG score, *n (%)*	
1	553 (48·4)
2	235 (20·6)

Notes: Percentages are calculated relative to the total number of subjects in the mITT analysis set in each group.

Appendix Table 2. Distribution of renal function according to cancer stage and site

	eGFR* <60 n/N (%)	eGFR* ≥60 n/N (%)		eGFR* <50 n/N (%)	eGFR* ≥50 n/N (%)
Locally advanced or metastatic cancer, *n (%)*	182 / 275 (66·2)	597 / 867 (68·9)		105 / 150 (70·0)	674 / 992 (67·9)
ECOG score, *n (%)*					
1	135 / 275 (49·1)	418 / 867 (48·2)		76 / 150 (50·7)	477 / 992 (48·1)
2	73 / 275 (26·5)	162 / 867 (18·7)		41 / 150 (27·3)	194 / 992 (19·6)
Site of cancer, *n (%)*					
Lung	50 / 275 (18·2)	150 / 867 (17·3)		20 / 150 (13·3)	180 / 992 (18·1)
Colorectal	48 / 275 (17·5)	183 / 867 (21·1)		23 / 150 (15·3)	208 / 992 (21·0)
Upper gastrointestinal	11 / 275 (4·0)	43 / 867 (5·0)		5 / 150 (3·3)	49 / 992 (4·9)
Pancreatic or Hepatobiliary	17 / 275 (6·2)	69 / 867 (8·0)		12 / 150 (8·0)	74 / 992 (7·5)
Breast	34 / 275 (12·4)	119 / 867 (13·7)		19 / 150 (12·7)	134 / 992 (13·5)
Genitourinary	49 / 275 (17·8)	88 / 867 (10·1)		30 / 150 (20·0)	107 / 992 (10·8)
Gynecological	30 / 275 (10·9)	88 / 867 (10·1)		21 / 150 (14·0)	97 / 992 (9·8)
Head and Neck	1 / 275 (0·4)	21 / 867 (2·4)		0 / 150 (0·0)	22 / 992 (2·2)
Bone/Soft Tissue	2 / 275 (0·7)	16 / 867 (1·8)		1 / 150 (0·7)	17 / 992 (1·7)
Skin - Melanoma	5 / 275 (1·8)	6 / 867 (0·7)		3 / 150 (2·0)	8 / 992 (0·8)
Hematologic malignancy	23 / 275 (8·4)	60 / 867 (6·9)		15 / 150 (10·0)	68 / 992 (6·9)
Other	4 / 275 (1·5)	23 / 867 (2·7)		1 / 150 (0·7)	26 / 992 (2·6)

*mL/min/1·73m^2

Appendix Table 3. Event rates by CKD stage according to different formulas

	MB rate (%)				VTE rate (%)		
CKD stage by formula	CKD-EPI	MDRD	Cockroft Gault		CKD-EPI	MDRD	Cockroft Gault
I	4·1	4·3	4·2		8·8	8·9	9·2
II	3·4	3·1	3·4		6·1	6·0	5·6
IIIa	4·2	4·5	3·3		6·9	5·7	5·5
IIIb+IV	4·6	4·2	5·3		1·5	0	4·3

Appendix Table 4. Description of study outcome events

	Number of Events		eGFR <60 mL/min/1·73m² n/N (%)	eGFR ≥60 mL/min/1·73m² n/N (%)		eGFR <50 mL/min/1·73m² n/N (%)	eGFR ≥50 mL/min/1·73m² n/N (%)
Major bleeding, overall	44		11/275 (4·0)	33/867 (3·8)		7/150 (4·7)	37/992 (3·7)
ICH	2		0/11 (0·0)	2/33(6·1)		0/7 (0·0)	2/37(5·4)
GI	20		3/11 (27·3)	17/33(51·5)		2/7 (28·6)	18/37(48·6)
GU	5		2/11 (18·2)	3/33(9·1)		2/7 (28·6)	3/37(8·1)
Muscular/skin	2		2/11 (18·2)	0/33(0·0)		1/7 (14·3)	1/37(2·7)
Other	16		4/11 (36·4)	12/33(36·4)		2/7 (28·6)	14/37(37·8)
Recurrent VTE	78		14/275 (5·1)	64/867 (7·4)		6/150 (4·0)	72/992 (7·3)
DVT	28		7/14 (50·0)	21/64 (32·8)		4/6 (66·7)	24/72 (33·3)
PE	51		7/14 (50·0)	44/64 (68·8)		2/6 (33·3)	49/72 (68·1)
Clinically relevant non-major bleeding, overall	87		26/275 (9·5)	61/867 (7·0)		12/150 (8·0)	75/992 (7·6)
GI	26		5/26 (19·2)	21/61 (34·4)		2/12 (16·7)	24/75 (32·0)
GU	29		12/26 (46·2)	17/61 (27·9)		7/12 (58·3)	22/75 (29·3)
Muscular/skin	1		0/26 (0·0)	1/61 (1·6)		0/12 (0·0)	1/75 (1·3)
Other	36		11/26 (42·3)	25/61 (41·0)		3/12 (25·0)	33/75 (44·0)

Patient 11123 (eGFR >= 60), reported one DVT and one PE event at the same day. One MB/CRNMB can have more than one site of bleeding.

For the overall data: n = number of patients with event. N = total number of subjects. For bleeding sites: n = number of patients with the specific site of bleeding. N = number of subjects with major bleeding. For VTE type: n = number of patients with specific type of VTE. N = number of subjects with VTE event.

ICH=intracranial hemorrhage; GI=gastrointestinal; GU= genitourinary.

Appendix Table 5. Variation of renal function over time*

Stage of RI at baseline	N patients with RI deteriorating of ≥1 stage from baseline value	N patients with RI improving of ≥1 stage from baseline value
1	126 (11·0)	0 (0·0)
2	102 (8·9)	90 (7·9)
3a	45 (3·9)	69 (6·1)
3b	15 (1·3)	37 (3·2)

* Each available value of eGFR over the study is considered in this table, therefore patients may experience both RI improving and deteriorating of >=1 stage from baseline.

Appendix Table 6. Multivariate analysis for determinants of mean l_n(eGFR) over time

Variable	Estimate	SE	95% CI		p
Follow up (days)	-0·00021	0·000181	-0·00056	0·000147	0·2516
Baseline age (years)	-0·01970	0·000824	-0·02132	-0·018080	< 0·0001
Treatment for cancer at the time of inclusion or within previous 6 months	0·05038	0·02639	0·00140	0·10220	0·0435

Estimated regression parameters, 95% confidence intervals (95% CI), standard errors (SE), p-values

Notes: All patients in mITT set with an available baseline value of eGFR are considered in this table.

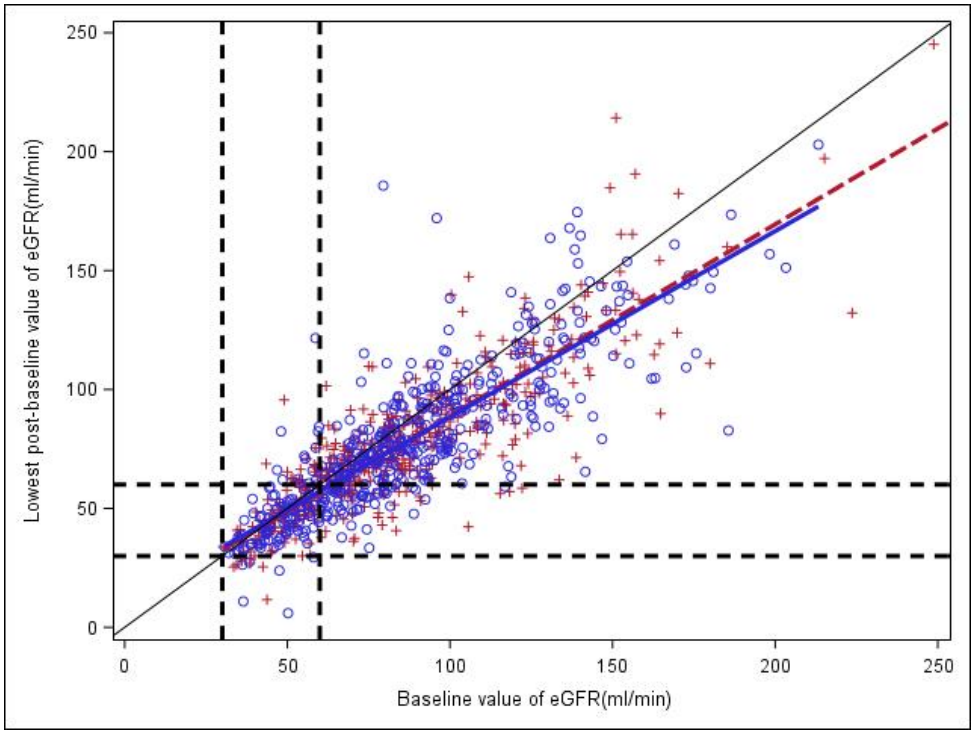
Missing values in eGFR post-baseline measurements were replaced using LOCF method.

A multivariate regression model for repeated measures was implemented, with ln(eGFR) as dependent variable.

Appendix Table 7. Variation of renal function over time and study outcome events

Study outcome events	RI deteriorating of ≥1 stage from baseline value		RI improving of ≥1 stage from baseline value	
	Yes (N=288)	No (N=854)	Yes (N=196)	No (N=946)
Major bleeding, n (%)	8 (2·8)	36 (4·2)	2 (1·0)	42 (4·4)
Recurrent VTE, n (%)	8 (2·8)	70 (8·2)	4 (2·0)	74 (7·8)
Clinically relevant non-major, n (%)	11 (3·8)	76 (8·9)	7 (3·6)	80 (8·5)
Major bleeding or recurrent VTE, n (%)	14 (4·9)	102 (11·9)	5 (2·6)	111 (11·7)

Appendix Figure 1. Variation of renal function during the study in patients randomized to apixaban or dalteparin



Lowest eGFR value (calculated by CG formula) during study treatment period versus baseline eGFR in patients given apixaban (+) or dalteparin (O) in mITT population. The solid black diagonal line is the line of identity (y = x). Linear regression lines, i.e. the solid blue diagonal line for patients receiving dalteparin and the red dashed diagonal line for those receiving apixaban, have been added to indicate trends. The black dashed lines signify eGFR 30 ml/min and eGFR 60 ml/min.

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