

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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Abstract

The effect of renal impairment (RI) on risk of bleeding and recurrent thrombosis in cancer patients treated with direct oral anticoagulants for venous thromboembolism (VTE) is undefined. We ran a prespecified analysis of the randomized Caravaggio study to evaluate the role of RI as a risk factor for bleeding or recurrence in patients treated with dalteparin or apixaban for cancer-associated VTE. RI was graded as moderate (creatinine clearance between 30-59 mL/minute; 275 patients) and mild (between 60-89 mL/minute; 444 patients). In the 1142 patients included in this analysis, the incidence of major bleeding was similar in patients with moderate vs. no or mild RI (HR 1.06-95% CI: 0.53-2.11), with no difference in the relative safety of apixaban and dalteparin. Recurrent VTE was not different in moderate vs. no or mild RI (HR=0.67, 95% CI: 0.38-1.20); in moderate RI, apixaban reduced recurrent VTE compared to dalteparin (HR=0.27, 95% CI: 0.08-0.96; P for interaction 0.1085). At multivariate analysis, no association was found between variation of renal function over time and major bleeding or recurrent VTE. Advanced or metastatic cancer was the only independent predictor of major bleeding (HR=2.84, 95% CI: 1.20-6.71), with no effect of treatment with apixaban or dalteparin. In our study, in cancer patients treated with apixaban or dalteparin, moderate RI was not associated with major bleeding or recurrent VTE. In patients with moderate renal failure, the safety profile of apixaban was confirmed with the potential for improved efficacy in comparison to dalteparin. ClinicalTrials.gov identifier: NCT03045406.

Introduction

The treatment of venous thromboembolism (VTE) in cancer patients is challenging due to the high risk of recurrent VTE and bleeding.^{1,2} In these patients, low molecular weight heparin (LMWH) was shown to reduce the rate of recurrent VTE in comparison to vitamin K antagonists, without increasing bleeding complications.^{3,4} Randomized studies have shown that the direct oral anti-Xa agents edoxaban, rivaroxaban and apixaban are non-inferior to dalteparin in the treatment of VTE in cancer patients.⁵⁻⁸ Hence, major international guidelines have recently considered direct oral anti-Xa agents as an alternative to LMWH for the treatment of cancer-associated VTE.⁹⁻¹¹

Renal impairment (RI) was independently associated with an increase of approximately 40% in the risk of major bleeding (4.6 vs. 2.4% person-years, adjusted hazard ratio= 1.40; 95% CI: 1.03-1.90) and recurrent thromboembolism (6.6 vs. 5.0% person-years, adjusted hazard ratio= 1.40; 95% CI: 1.10-1.77) in patients receiving anticoagulants for the treatment of VTE.¹² The association between RI and the risk for recurrent VTE and bleeding was assessed in cancer patients receiving LMWH or vitamin K antagonists in observational studies and in sub-analyses of randomized studies.¹³⁻¹⁶ In these sub-analyses, the efficacy to safety profile of LMWH in comparison to warfarin was similar in cancer patients with and without RI.¹³⁻¹⁶ The effect of RI on the risk of recurrent VTE and bleeding

in patients with cancer-associated VTE treated with direct oral anti-Xa agents is uncertain.¹⁷ As direct anti-Xa agents have a variable but substantial degree of renal excretion, RI may be associated with increased plasma levels of these agents with potential for increased bleeding risk. In phase III randomized controlled trials of direct oral anti-coagulants for the treatment of VTE in the general population, no difference in recurrent VTE (RR=0.70, 95% CI: 0.43–1.15) but a significant reduction in major bleeding (RR= 0.51, 95% CI: 0.26–0.99) was seen in comparison with vitamin K antagonists in patients with creatinine clearance of 30–49 mL/min.¹⁸

The effect of RI on the efficacy and safety profile of the direct oral anticoagulants in the four randomized clinical studies of oral anti-Xa agents in patients with cancer associated VTE is unknown. In these studies, although patients with a creatinine clearance < 30 mL/min were excluded, a consistent proportion of patients had mild or moderate RI.^{5–8}

In the Caravaggio study, oral apixaban was found to be non-inferior to subcutaneous dalteparin for the treatment of cancer-associated VTE.^{8,19} The rate of major bleeding was similar with apixaban and dalteparin. The aim of this pre-specified analysis in patients included in the Caravaggio study was to assess the association between RI and bleeding or recurrent VTE. The effect of both baseline renal function and its variations during treatment with apixaban or dalteparin was evaluated for the association with major bleeding and recurrent VTE.

Methods

Caravaggio was a multinational, prospective, randomized, open-label, with blinded end-point evaluation (PROBE), non-inferiority study aimed at assessing whether oral apixaban was non-inferior to dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer. The rationale, design and results of the Caravaggio study were described previously.^{8,19}

The trial was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol and its amendments were approved by the institutional review board or ethics committee at each trial center. All the patients provided written informed consent.

Consecutive adult patients with cancer who had symptomatic or incidental acute proximal DVT or PE were randomized to receive oral apixaban (10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or subcutaneous dalteparin (200 IU per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily) for 6 months. Inclusion and exclusion

Table 1. Renal impairment stage classification.

RI stage	Severity classification	eGFR*
I	Preserved	≥ 90 mL/min
II	Mild reduction	<90 mL/min and ≥60 mL/min
III	Moderate reduction	<60 mL/min and ≥30 mL/min
IIIa	-	<60 mL/min and ≥45 mL/min
IIIb	-	<45 mL/min and ≥30 mL/min
IV	Severe reduction	< 30 mL/min and ≥15 mL/min
V	Pre-dialysis	<15 mL/min

*eGFR based on the Cockcroft-Gault equation. RI: renal impairment; eGFR: estimated glomerular filtration rate.

criteria are reported in the *Online Supplementary Data*. Only patients with baseline creatinine assessment at randomization were included in this prespecified analysis. Patients were excluded in case of a creatinine clearance <30 mL/min based on the Cockcroft Gault equation. RI was classified into the conventional five stages as indicated in Table 1.²⁰

Study outcomes

This analysis has two co-primary outcomes: major bleeding and recurrent VTE defined according to Caravaggio criteria and occurring from randomization to day 180 (see *Online Supplementary Data*).

Secondary study outcomes were clinically relevant non-major bleeding and a composite of major bleeding and recurrent VTE.

Follow-up and measurements

Renal function was calculated by three accepted methods, the Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD) equations (see *Online Supplementary Data*).^{21–23}

Patients were also categorized on the basis of estimated glomerular filtration rate (eGFR) as having no or mild RI (eGFR of 60 mL/min or higher) vs. moderate RI (eGFR lower than 60 mL/min) and having eGFR of ≥50 mL/min vs. <50 mL/min. The management of study treatments according to creatinine clearance was dictated by the protocol.

Statistical analysis

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

- (i) a 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/min) at inclusion in the study;
- (ii) proportional hazards model for the time to study outcome events with eGFR (according to the Cockcroft-Gault formula) as a time-varying covariate. We analysed log-

Table 2. Baseline renal function in patients randomized to apixaban or dalteparin.

	All patients N=1142 (%)	Apixaban N=573 (50.2%)	Dalteparin N=569 (49.8%)
Baseline eGFR			
Cockcroft-Gault, mean ± SD	85.2 ± 33.9	84.8 ± 34.4	85.6 ± 33.5
CKD-EPI, mean ± SD	78.3 ± 20.8	78.5 ± 20.7	78.1 ± 20.8
MDRD, mean ± SD	87.0 ± 33.9	86.7 ± 32.3	86.4 ± 30.6
CKD stage according to Cockcroft-Gault formula, n (%)			
I (eGFR ≥90 mL/min)	423 (37.0)	201 (35.1)	222 (39.0)
II (eGFR <90 mL/min and ≥60 mL/min)	444 (38.9)	235 (41.0)	209 (36.7)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	181 (15.8)	97 (16.9)	84 (14.8)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	94 (8.2)	40 (7.0)	54 (9.5)
CKD stage according to CKD-EPI, n (%)			
I (eGFR ≥90 mL/min)	364 (31.9)	176 (30.7)	188 (33.0)
II (eGFR <90 mL/min and ≥60 mL/min)	524 (45.9)	270 (47.1)	254 (44.6)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	189 (16.5)	97 (16.9)	92 (16.2)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	62 (5.4)	29 (5.1)	33 (5.8)
IV (eGFR <30 mL/min and ≥15 mL/min)	3 (0.3)	1 (0.2)	2 (0.4)
CKD stage according to MDRD, n (%)			
I (eGFR ≥90 mL/min)	439 (38.4)	219 (38.2)	220 (38.7)
II (eGFR <90 mL/min and ≥60 mL/min)	479 (41.9)	242 (42.2)	237 (41.7)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	176 (15.4)	92 (16.1)	84 (14.8)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	46 (4.0)	19 (3.3)	27 (4.7)
IV (eGFR <30 mL/min and ≥15 mL/min)	2 (0.2)	1 (0.2)	1 (0.2)

Percentages are calculated relative to the total number of subjects in the modified intention-to-treat analysis set in each group. eGFR: estimated glomerular filtration rate; SD: standard deviation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modified Diet and Renal Disease.

transformed eGFR ($Y = \log(\text{eGFR})$) data throughout, as previously described for this kind of analyses.²⁴

The final set of covariates for the multivariate analysis was selected among those with a *P*-value of 0.15 or less at univariate analyses.

For comparison of proportions, deterioration of renal function was defined as a decrease in eGFR leading to a change of at least one stage from baseline values, according to the Cockcroft-Gault formula. Because subgroup analyses in the present study were exploratory, the *P* values were not adjusted for multiple comparisons and should be interpreted with caution.

Analyses were performed with SAS software (version 9.4). Other details are reported in the *Online Supplementary Data*.

Results

Overall, 1142 patients were included in this analysis (*Online Supplementary Data, Table S1*). Thirteen patients from the original Caravaggio study were excluded due to lack of renal function assessment at inclusion in the study - one of whom reported major bleeding during the study - or for an eGFR lower than 30 mL/min at inclusion. Mean baseline eGFR according to the Cockcroft-Gault, CKD-EPI and MDRD equations are reported in Table 2. At inclusion in the

study, 37% of patients had stage 1, 39% stage 2 and 24% stage 3 RI; 8.2% had stage 3b RI with eGFR between 30 and 44 mL/min according to the Cockcroft-Gault formula. CKD-EPI classified a numerically lower proportion of patients in stage 1 and a numerically higher proportion in stage 2 RI compared to Cockcroft-Gault or MDRD equations. Mean baseline eGFR, as well as distribution across different stages of RI, were similar in patients randomized to apixaban or dalteparin whatever the formula used for calculation of eGFR (Table 2). At inclusion in the study, 23.9% and 24.3% of patients randomized to receive apixaban and dalteparin had stage 3 RI according to the Cockcroft-Gault formula, respectively.

The distribution of RI stage according to cancer stage or site is reported in *Online Supplementary Data, Table S2*.

Renal function and study outcome events

The mean eGFR at baseline was similar in patients who experienced a major bleeding event compared to patients who did not experience one during the study (Table 3). At inclusion in the study, 25% and 24% of patients who experienced or did not experience a major bleed during the study had stage 3 RI, respectively. Event rates by CKD stage calculated by different formulas are reported in *Online Supplementary Data, Table S3*.

The incidence of major bleeding was similar in patients with moderate RI vs. patients with no or mild RI (4.0 vs.

Table 3. Baseline characteristics of the study population according to study outcome groups.

	All patients N= 1142 (%)	Patients with major bleeding N= 44 (3.9 %)	Patients without major bleeding N = 1098 (96.1 %)	Patients with recurrent VTE N= 78 (6.8%)	Patients without recurrent VTE N = 1064 (93.2%)
Age, years					
Mean ± SD	67.7±11.1	67.9±8.2	67.7±11.2	65.5±10.2	67.9±11.2
> 75 years, N (%)	296 (25.9)	9 (20.5)	287 (26.1)	14 (17.9)	282 (26.5)
Range	21-93	51-86	21-93	42-87	21-93
Female gender, N	579	20	559	38	541
BMI, mean ± SD	26.7±5.2	25.6±4.1	26.8±5.2	26.5±5.2	26.8±5.2
Baseline eGFR					
Cockroft Gault, mean ± SD	85.2±33.9	81.5±29.1	85.4±34.1	96.1±39.4	84.4±33.4
CKD-EPI, mean ± SD	78.3±20.8	79.3±22.0	78.2±20.7	84.8±21.1	77.8±20.7
MDRD, mean ± SD	86.7±32.3	89.2±36.6	86.6±32.1	98.4±50.2	85.8±30.4
CKD stage according to Cockroft-Gault formula, N (%)					
I (eGFR ≥90 mL/min)	423 (37.0)	18 (40.9)	405 (36.9)	39 (50.0)	405 (36.9)
II (eGFR <90 mL/min and ≥60 mL/min)	444 (38.9)	15 (34.1)	429 (39.1)	25 (32.1)	429 (39.1)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	181 (15.8)	6 (13.6)	175 (15.9)	10 (12.8)	175 (15.9)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	94 (8.2)	5 (11.4)	89 (8.1)	4 (5.1)	89 (8.1)
CKD stage according to CKD-EPI, N (%)					
I (eGFR ≥90 mL/min)	364 (31.9)	15 (34.1)	349 (31.8)	32 (41.0)	332 (31.2)
II (eGFR <90 mL/min and ≥60 mL/min)	524 (45.9)	18 (40.9)	506 (46.1)	32 (41.0)	492 (46.2)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	189 (16.5)	8 (18.2)	181 (16.5)	13 (16.7)	176 (16.5)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	62 (5.4)	2 (4.5)	60 (5.5)	1 (1.3)	61 (5.7)
IV (eGFR <30 mL/min and ≥15 mL/min)	3 (0.3)	1 (2.3)	2 (0.2)	0 (0.0)	3 (0.3)
CKD stage according to MDRD, N (%)					
I (eGFR ≥90 mL/min)	439 (38.4)	19 (43.2)	420 (38.3)	39 (50.0)	400 (37.6)
II (eGFR <90 mL/min and ≥60 mL/min)	479 (41.9)	15 (34.1)	464 (42.3)	29 (37.2)	450 (42.3)
IIIa (eGFR <60 mL/min and ≥45 mL/min)	176 (15.4)	8 (18.2)	168 (15.3)	10 (12.8)	166 (15.6)
IIIb (eGFR <45 mL/min and ≥30 mL/min)	46 (4.0)	1 (2.3)	45 (4.1)	0 (0.0)	46 (4.3)
IV (eGFR <30 mL/min and ≥15 mL/min)	2 (0.2)	1 (2.3)	1 (0.1)	0 (0.0)	2 (0.2)
Locally advanced or metastatic cancer, N (%)	779 (68.2)	38 (85.4)	741 (67.5)	38 (85.4)	741 (67.5)
ECOG score, N (%)					
1	553 (48.4)	20 (45.5)	533 (48.5)	20 (45.5)	533 (48.5)
2	235 (20.6)	14 (31.8)	221 (20.1)	14 (31.8)	221 (20.1)

MB: major bleeding. *according to Cockroft-Gault formula. VTE: venous thromboembolism; SD: standard deviation; GFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modified Diet and Renal Disease; CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group.

3.8%; HR=1.06, 95% CI: 0.53-2.11) (Table 4). These results were confirmed in patients randomized to receive apixaban (3.6 vs. 3.7%) or dalteparin (4.3 vs. 3.9%). Rates of major bleeding were similar in patients randomized to apixaban or dalteparin in the two groups of moderate RI and no or mild RI (*P*-value for interaction 0.8819). These results were confirmed in patients with eGFR below or above 50 mL/min.

A numerically lower rate of recurrent VTE was observed in patients with moderate RI as compared to patients with no or mild RI (HR=0.67, 95% CI: 0.38-1.20). Among patients randomized to apixaban, a not significant 69% reduction

of recurrent VTE was observed in those with moderate RI compared to those with no or mild RI (2.2 vs. 6.7%; HR=0.31, 95% CI: 0.09-1.03). No difference in recurrent VTE was observed with dalteparin in patients with moderate RI vs. no or mild RI. A lower incidence of recurrent VTE was observed in patients with moderate RI randomized to apixaban compared to dalteparin (2.2 vs. 8.0%; HR=0.27, 95% CI: 0.08-0.96, *P*-value for interaction 0.1085). The reduction of recurrent VTE with apixaban compared to dalteparin was confirmed in patients with eGFR lower than 50 mL/min.

A numerically higher rate of clinically relevant non-major

Table 4. Frequency of study outcome events based on baseline estimated glomerular filtration rate calculated according to the Cockcroft-Gault formula.

	Major bleeding			HR (95% CI)	P for interaction		Major bleeding			HR (95% CI)	P for interaction
	Overall	Apixaban	Dalteparin				Overall	Apixaban	Dalteparin		
eGFR <60*	11/275	5/137	6/138	0.84	0.8819	eGFR <50*	7/150	3/68	4/82	0.85	0.9757
n/N, %	4.0	3.6	4.3	0.26-2.71		n/N %	4.7	4.4	4.9	0.19-3.80	
eGFR ≥60*	33/867	16/436	17/431	0.92		eGFR ≥50*	37/992	18/505	19/487	0.91	
n/N, %	3.8	3.7	3.9	0.47-1.83		n/N, %	3.7	3.6	3.9	0.48-1.73	
HR	1.06	1.02	1.11			HR	1.26	1.24	1.28		
95% CI	0.53-2.11	0.37-2.79	0.43-2.83			95% CI	0.56-2.84	0.37-4.20	0.43-3.79		
	Recurrent VTE			HR (95% CI)	P for interaction		Recurrent VTE			HR (95% CI)	P for interaction
	Overall	Apixaban	Dalteparin				Overall	Apixaban	Dalteparin		
eGFR <60*	14/275	3/137	11/138	0.27	0.1085	eGFR <50*	6/150	0/68	6/82	N.A.	N.A.
n/N, %	5.1	2.2	8.0	0.08-0.96		n/N %	4.0	0.0	7.3		
eGFR ≥60*	64/867	29/436	35/431	0.82		eGFR ≥50*	72/992	32/505	40/487	0.76	
n/N, %	7.4	6.7	8.1	0.50-1.33		n/N (%)	7.3	6.3	8.2	0.48-1.22	
HR	0.67	0.31	0.97			HR	0.53	N.A.	0.87		
95% CI	0.38-1.20	0.09-1.03	0.50-1.91			95% CI	0.23-1.22		0.37-2.04		
	Recurrent VTE or major bleeding			HR 95% CI	P for interaction		Recurrent VTE or major bleeding			HR (95% CI)	P for interaction
	Overall	Apixaban	Dalteparin				Overall	Apixaban	Dalteparin		
eGFR <60*	23/275	8/137	15/138	0.53	0.3675	eGFR <50*	12/150	3/68	9/82	0.39	0.2947
n/N, %	8.4	5.8	15/138 10.9	0.23-1.24		n/N %	8.0	4.4	11.0	0.12-1.40	
eGFR ≥60*	93/867	42/436	51/431	0.81		eGFR ≥50*	104/992	47/505	57/487	0.78	
n/N, %	10.7	9.6	11.8	0.54-1.21		n/N %	10.5	9.3	11.7	0.53-1.15	
HR	0.76	0.59	0.91			HR	0.74	0.45	0.92		
95% CI	0.48-1.21	0.27-1.26	0.51-1.61			95% CI	0.41-1.34	0.14-1.46	0.46-1.86		
	Clinically relevant non-major bleeding			HR (95% CI)	P for interaction		Clinically relevant non-major bleeding			HR (95% CI)	P for interaction
	Overall	Apixaban	Dalteparin				Overall	Apixaban	Dalteparin		
eGFR <60*	26/275	18/137	8/138	2.35	0.2364	eGFR <50*	12/150	5/68	7/82	0.87	0.2682
n/N, %	9.5	13.1	5.8	1.01-5.45		n/N, %	8.0	7.4	8.5	0.27-2.76	
eGFR ≥60*	61/867	34/436	27/431	1.26		eGFR ≥50*	75/992	47/505	28/487	1.65	
n/N, %	7.0	7.8	6.3	0.76-2.09		n/N, %	7.6	9.3	5.7	1.03-2.63	
HR	1.35	1.67	0.94			HR	1.05	0.76	1.53		
(95% CI)	0.85-2.12	0.95-2.94	0.42-2.08			(95% CI)	0.57-1.93	0.31-1.90	0.66-3.56		
	Major bleeding or CRNMB			HR (95% CI)	P for interaction		Major bleeding or CRNMB			HR (95% CI)	P for interaction
	Overall	Apixaban	Dalteparin				Overall	Apixaban	Dalteparin		
eGFR <60*	36/275	23/137	13/138	1.83	0.2011	eGFR <50*	18/150	8/68	10/82	0.96	0.5026
n/N, %	13.1	16.8	9.4	0.92-3.62		n/N, %	12.0	11.8	12.2	0.38-2.40	

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eGFR $\geq 60^*$	89/867	46/436	43/431	1.06		eGFR $\geq 50^*$	107/992	61/505	46/487	1.29	
n/N, %	10.3	10.6	10.0	0.70-1.61		n/N, %	10.8	12.1	9.4	0.88-1.89	
HR	1.28	1.61	0.95			HR	1.11	0.95	1.34		
95% CI	0.87-1.89	0.98-2.64	0.51-1.78			95% CI	0.67-1.84	0.46-1.98			

All patients in the modified intention-to-treat set with an available baseline value of estimated glomerular filtration rate (eGFR) are considered in this table. An eGFR cut-off of 50 mL per minute was used in some phase III studies with direct oral anticoagulants. The hazard ratios (HR) (last column of the table) are adjusted for the competing risk of death unrelated to event by resorting to the Fine & Gray regression model using eGFR group, symptomatic vs. unsuspected VTE and active cancer vs. history of cancer as covariates. The HR for comparison between dalteparin and apixaban are adjusted for the competing risk of death unrelated to event by resorting to the Fine & Gray regression model using treatment group, symptomatic vs. unsuspected venous thromboembolism and active cancer vs. history of cancer as covariates. n: number of patients with events; N: total number of patients in each category. HR: hazard ratio; 95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate; VTE: venous thromboembolism; CRNMB: clinically relevant non-major bleeding.

bleeding was observed in patients with moderate RI vs. no or mild RI, and this was mainly accounted for by patients randomized to receive apixaban (Table 4). In patients with moderate RI, a two-fold increase in the incidence of clinically relevant non-major bleeding was observed with apixaban in comparison to dalteparin (P -value for interaction 0.2364). Both major and clinically relevant non-major bleeding were more common at genito-urinary sites in patients with reduced eGFR (either lower than 60 or 50 mL/min) in comparison to patients with no or mild RI; both major and clinically relevant non-major bleeding were more common at gastrointestinal sites in patients with no or mild RI (eGFR higher than 60 or 50 mL/min) in comparison to patients with reduced eGFR (either lower than 60 or 50 mL/min) (*Online Supplementary Data, Table S4*).

Renal function over time and study outcome

During the six-month treatment period, 288 patients (25%) experienced a deterioration of eGFR leading to a change of at least one stage from baseline values. This deterioration occurred in similar proportions of patients, regardless of the baseline eGFR stage (*Online Supplementary Data, Table S5*). Age at inclusion was associated with a deterioration of eGFR over time; treatment for cancer at inclusion or within the previous 6 months was associated with increasing eGFR over time (*Online Supplementary Data, Table S6*). No association was found between ECOG or cancer that was locally advanced/metastatic or unsuspected vs. symptomatic VTE or active cancer vs. history of cancer and eGFR over time. Variation of renal function over time was similar in patients randomized to receive apixaban or dalteparin (*Online Supplementary Data, Figure S1*).

A major bleed occurred in 2.8 and 4.2% of patients having and not having deterioration of eGFR leading to a change of at least one stage from baseline values, respectively (*Online Supplementary Data, Table S7*). Recurrent VTE occurred in 2.8% and 8.2% of patients with or without deterioration of eGFR leading to a change of at least one stage from baseline values, respectively.

Multivariate analyses using renal function as a time-varying covariate and with death unrelated to an event as a competing risk were performed for study outcome events. Recurrent or locally-advanced or metastatic cancer (HR=2.84, 95% CI: 1.20-6.71) was an independent predictor of major bleeding (Table 5). No independent association was found between variation of renal function over time and major bleeding or recurrent VTE. A not significant association was found between recurrent or locally-advanced or metastatic cancer (HR=1.65, 95% CI: 0.95-2.86) or treatment with apixaban (HR=0.66, 95% CI: 0.42-1.05) and recurrent VTE. No association between variation of renal function over time and the risk for recurrent VTE was observed.

Discussion

Renal insufficiency occurs frequently in patients with cancer-associated VTE, with more than 60% of patients enrolled in the Caravaggio study having mild or moderate RI. RI was found not to be a risk factor for major bleeding or recurrent VTE in this population. No association was found between either moderate RI (eGFR lower than 60 mL/min) or defined by eGFR lower than 50 mL/min and major bleeding in patients randomized to apixaban or dalteparin. Apixaban appeared to reduce recurrent VTE in patients with moderate RI in comparison to dalteparin, with no effect on the incidence of major bleeding but a not significant increase in clinically relevant non-major bleeding. The efficacy to safety ratio of apixaban was similar to that of dalteparin in patients with normal renal function or mild RI. Recurrent or locally advanced or metastatic cancer was the only independent predictor for major bleeding in this population of patients with cancer-associated VTE.

RI is a common condition in the general adult population and is prevalent in patients with cancer. In a single-center cohort study, about two-thirds of patients with solid cancer had abnormal renal function (eGFR <90 mL/min/1.73 m²); 15% had moderate RI and 1% to 2% had severe RI.²⁵ In the CLOT study, 24% of patients with

Table 5. Risk factors for major bleeding, recurrent venous thromboembolism or clinically relevant non-major bleeding according to a Cox model with time-varying covariates.

	HR	95%CI	P
Risk factors for major bleeding			
eGFR* over time	0.57	0.21-1.55	0.26
Baseline age (years)	0.99	0.97-1.01	0.41
Treatment for cancer at the time of inclusion or within previous 6 months	1.45	0.67-3.14	0.35
Recurrent locally advanced or metastatic cancer	2.84	1.20-6.71	0.02
Treatment (reference Dalteparin) / Apixaban	0.96	0.53-1.75	0.89
Risk factors for recurrent VTE			
eGFR* over time	1.70	0.82-3.52	0.15
Baseline age (years)	0.99	0.97-1.01	0.48
Treatment for cancer at the time of inclusion or within previous 6 months	0.74	0.33-1.62	0.45
Recurrent locally advanced or metastatic cancer	1.65	0.95-2.86	0.08
Treatment (reference Dalteparin) / Apixaban	0.66	0.42-1.05	0.08
Risk factors for clinically relevant non-major bleeding			
eGFR* over time	1.18	0.61-2.28	0.63
Baseline age (years)	1.03	1.00-1.05	0.03
Treatment for cancer at the time of inclusion or within previous 6 months	1.07	0.59-1.98	0.83
Recurrent locally advanced or metastatic cancer	1.25	0.77-2.03	0.36
Treatment (reference Dalteparin) / Apixaban	1.52	0.99-2.35	0.08
Risk factors for major bleeding or recurrent VTE			
eGFR* over time	1.17	0.62-2.22	0.63
Baseline age (years)	0.99	0.97-1.01	0.23
Treatment for cancer at the time of inclusion or within previous 6 months	1.08	0.62-1.86	0.80
Recurrent locally advanced or metastatic cancer	1.99	1.24-3.21	0.004
Treatment (reference Dalteparin) / Apixaban	0.74	0.51-1.07	0.11

All patients in the modified intention-to-treat set with an available baseline value of estimated glomerular filtration rate (eGFR) are considered in this table. *eGFR included in the analyses as log-transformed eGFR (see methods section). HR: hazard ratio; 95% CI: 95% confidence interval; VTE: venous thromboembolism.

cancer-associated VTE had eGFR lower than 60 mL/min, with 22% having moderate RI and 2% severe RI.¹⁶ In the Catch study, 15% of patients with cancer-associated VTE had eGFR lower than 60 mL/min at inclusion;¹⁵ RI was more common in patients with gynecological and genitourinary malignancies. In the EINSTEIN VTE studies, more than half of the patients identified as having cancer had creatinine clearance <80 mL/min and 15% had creatinine clearance <50 mL/min.²⁶ In the Amplify VTE study, patients with active cancer or history of cancer more commonly had creatinine clearance lower than 50 mL/min in comparison to non-cancer patients.²⁷ Overall, our results showing a prevalence of moderate RI greater than 20% in patients with cancer-associated VTE are consistent with those from previous studies in this setting. The clinical relevance of our observation is related to the hypothesis that RI could reduce renal excretion of both LMWH and direct anti-Xa anticoagulants and potentially lead to anticoagulant overdosing and an increase in bleeding complications. Whether dose reduction or dose adjustment of LMWH based on anti-Xa activity are valid options to avoid an in-

crease in bleeding risk in patients with severe RI is uncertain.^{28,29} The evidence in favor of these approaches is limited both in the general population of patients with VTE and in cancer patients with VTE. To date, the optimal anti-coagulant agent and regimen in patients with severe renal failure is undefined. Among LMWH, dalteparin seems to be associated with acceptable bleeding risk in patients with RI.^{16,30,31} Among direct oral anti-Xa anticoagulants, dose reduction for patients with RI was evaluated for edoxaban in the treatment of VTE. No dose adjustment has been tested in clinical trials for the treatment of VTE with apixaban or rivaroxaban. Our study shows that the current regimen of apixaban developed and approved for the treatment of VTE is effective and safe in cancer patients with moderate RI.

We found no association between RI and bleeding or thromboembolic risk in patients with cancer-associated VTE randomized to receive apixaban or dalteparin. These findings are in contrast with those from previous studies in the general population of patients with acute VTE as well as in cancer patients included in a randomized study

that compared tinzaparin or dalteparin with warfarin.^{12,15,16} These studies showed an increased risk of bleeding in patients with moderate RI in comparison with patients with no or mild RI. In two of these studies, RI was also associated with an increase in recurrent VTE.^{12,15} A comparison of recent studies with anti-Xa agents for the treatment of cancer-associated VTE is difficult as only about 7% of patients in the HOKUSAI VTE cancer study had moderate RI, with no RI data available for the Select-D study.^{5,6}

This analysis shows similar safety profiles of apixaban and dalteparin across different stages of RI in terms of major bleeding. An increase in clinically relevant non-major bleeding was observed with apixaban compared to dalteparin in patients with moderate RI. This difference was mainly driven by an increase in apixaban-associated genito-urinary bleeding in patients with moderate RI. An increase in genito-urinary bleeding was reported in the main Caravaggio study and we have now added information that it is related to moderate RI.⁸ Whether this increase in genito-urinary bleeding is to be related to the presence of genito-urinary cancer, to the accumulation of study drugs at the urinary site or, rather, to the use of specific anti-cancer agents remains undefined.³² Indeed, as these findings derive from subgroup analyses and refer to limited numbers of events, they can only be regarded as hypothesis generating. In phase III trials with direct oral anticoagulants for the treatment of VTE, no effect of RI on efficacy was reported.^{17,18} Concerning the safety of direct oral anticoagulants, the favorable effect observed in the general population was confirmed across different stages of RI.

In our study in patients with cancer-associated VTE, about 25% of patients had a significant variation of renal function leading to change in eGFR stage. A previous study in patients with cancer-associated VTE reported similar rates of variation of renal function over time.¹⁵ Anticancer agents, particularly platinum-based agents, may affect renal function, potentially leading to deterioration of RI. In this case, patients with RI may require surveillance for periodical reassessment of renal function and bleeding risk.

In a subgroup meta-analysis on 1789 patients without cancer with creatinine clearance between 30 and 49 mL/min included in phase III trials in the treatment of VTE, no difference in terms of recurrent VTE (RR=0.70, 95% CI: 0.43–1.15) was reported in patients receiving direct oral anticoagulants vs. vitamin K antagonists (VKA); however, a significant reduction in major bleedings (RR=0.51, 95% CI: 0.26–0.99) was found.¹⁸ Similarly, in the four randomized clinical studies with oral anti-Xa agents for the treatment of cancer-associated VTE, no effect of renal function emerged on the efficacy and safety profile of these agents.^{5–8} Taken together, these data suggest that the oral anti-Xa agents could be used in patients with cancer-associated VTE and creatinine clearance 30–49 mL/min. Pa-

tients with a creatinine clearance <30 mL/min were excluded from phase III clinical trials on the treatment of cancer-associated VTE and no dose adjustment was scheduled for direct oral anticoagulants based on renal function in these patients, except for the studies with edoxaban. Data regarding safety and efficacy of direct oral anticoagulants in cancer patients with severe renal impairment are lacking. It is conceivable that, for patients with creatinine clearance <30 mL/min, treatment with unfractionated heparin may be preferred or, as an alternative, vitamin K antagonists can still be still an option. Despite being based on limited evidence, dose- and perhaps anti-Xa activity-adjusted LMWH might be considered.^{28,29,33,34} Further evidence is needed to define the optimal anticoagulant strategy for these patients.

Several equations are currently in use to non-invasively estimate eGFR. eGFR is an accepted index of renal function, regardless of the formula used for the calculation. The Cockcroft-Gault equation is, at present, the most widely used in clinical practice and was employed in phase III clinical trials with direct oral anticoagulants to calculate eGFR and adjust the dose of the oral anti-Xa agents. For this reason, the Cockcroft-Gault equation is commonly used to adjust dosing of direct oral anticoagulants in patients with atrial fibrillation. However, as this formula may overestimate eGFR, the CKD-EPI equation was developed to more accurately estimate eGFR across all ranges of renal function and was tested in sub-analyses of studies with direct oral anticoagulants.³⁵ Cockcroft-Gault, CKD-EPI and MDRD are all serum creatinine-based estimations of eGFR and depend on age and gender. Differences across equations emerged in our study between the Cockcroft-Gault and CKD-EPI equations concerning proportions of patients classified with stage I or stage II RI. The majority of reclassifications occurred in the group estimated as having normal renal function according to the Cockcroft-Gault equation. However, incidences of study outcome events in our study were similar in stages I and II RI, as calculated by different formulas.

Our study has some limits. In particular, 13 patients included in the Caravaggio study were excluded from this analysis due to the lack of baseline creatinine value at the time of inclusion or to the violation of the inclusion requirement necessitating creatinine clearance greater than 30 mL/min. The study was designed as an open-label randomized study. Investigators were aware of study treatment assignment and of creatinine clearance values over time. The management of study treatments according to creatinine clearance was dictated by the protocol, demonstrating that accurate management of anticoagulant treatment may avoid complications due to deterioration of renal function. Finally, our analysis cannot provide information on the efficacy and safety of apixaban and

dalteparin in patients with severe RI (creatinine clearance lower than 30 mL/min), as these patients were excluded from the Caravaggio study. Our study benefits from its randomized design with prospective assessments of renal function in a large population of cancer patients and the blind adjudication of all the study outcome events by an independent committee.

In conclusion, this analysis shows that a substantial proportion of cancer patients have RI when diagnosed with VTE, or experience a deterioration of renal function in the 6-month period beyond the index VTE. However, no effect of renal function at the initiation of anticoagulant treatment or of variation of renal function during anticoagulant treatment is associated with the risk for major bleeding or recurrent VTE in patients randomized to receive apixaban or dalteparin. Recurrent or locally-advanced or metastatic cancer was shown to be the only independent predictor of major bleeding in cancer patients with VTE. Clinically relevant non-major bleeding seems to be more common in patients with moderate RI receiving apixaban in comparison to dalteparin.

Disclosures

CB reports personal fees from Bayer HealthCare, Bristol Myers Squibb, and Daiichi Sankyo, outside the submitted work. RB reports personal fees from Bristol-Myers-Squibb, Pfizer, Bayer Healthcare, and LEO, outside the submitted work. GM has nothing to disclose. LB reports grants, personal fees and non-financial support from Bristol-Myers Squibb/Pfizer, grants and personal fees from Bayer, personal fees and non-financial support from Leo-Pharma,

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Contributions

CB, GM, RB and GA were responsible for the conception and design of the study or analysis and interpretation of data, or both. All authors contributed to drafting the manuscript or revising it critically for important intellectual content and provided final approval of the manuscript submitted.

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Data-sharing statement

Data collected for the study may be shared after approval of potential proposals by the Steering Committee and with a signed data-access agreement, and at least 6 months after manuscript publication.

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