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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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Title page

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

Results from the Caravaggio trial.

Running head: Apixaban and renal function in cancer-associated VTE

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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 run a prespecified analysis of the randomized Caravaggio study to evaluate the role of RI as 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 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.

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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 showed 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 about 40% increase 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 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 anticoagulants 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 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 per minute 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 criteria are reported in the 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 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: Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) (Supplementary data). [21-23]

Patients were also categorized as having no or mild RI (eGFR of 60 ml per minute or higher) vs. moderate RI (eGFR lower than 60 ml per minute) and having eGFR of ≥50 ml per minute vs. <50 ml per minute.

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.) 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. We analysed log-transformed eGFR (Y = log (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 1 stage from baseline values, according to the Cockroft-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 Supplementary data.

Results

Overall, 1142 patients were included in this analysis (Table 1 Supplementary data). Thirteen patients from the original Caravaggio study were excluded for lack of renal function assessment at inclusion in the study - one of whom reported a major bleeding during the study – or for an eGFR lower than 30 ml per minute at inclusion. Mean baseline eGFR according to the Cockroft 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 per minute according to the Cockroft-Gault formula. CKD-EPI classified a numerically lower proportion of patients in stage I and a numerically higher proportion in stage II RI compared to Cockroft-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 Cockroft-Gault formula, respectively.
The distribution of RI stages according to cancer stage or site is reported in Supplementary data Table 2.

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 it during the study (Table 3). At inclusion in the study, 25% and 24% of patients who experienced or did not experience a major bleeding during the study had stage 3 RI. Event rates by CKD stage calculated by different formulas are reported in Table 3 Supplementary data.
The Incidence of major bleeding was similar in patients with moderate RI vs. patients with no or mild RI (4.0 vs. 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 per minute.

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 per minute.

A numerically higher rate of clinically relevant non major 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 site in patients with reduced eGFR (either lower than 60 or 50 ml per minute) in comparison to patients with no or mild RI; both major and clinically relevant non major bleeding were more common at gastrointestinal site in patients with no or mild RI (eGFR higher than 60 or 50 ml per minute) in comparison to patients with reduced eGFR (either lower than 60 or 50 ml per minute) (Table 4 Supplementary data).

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 1 stage from baseline values. This deterioration occurred in similar proportions of patients, regardless of the baseline eGFR stage (Table 5 Supplementary data). 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 (Table 6 Supplementary data). 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 (Figure 1 Supplementary data).

A major bleeding occurred in 2.8 and 4.2% of patients having and not having deterioration of eGFR leading to a change of at least 1 stage from baseline values, respectively (Table 7 Supplementary data). Recurrent VTE occurred in 2.8 and 8.2% of patients with or without deterioration of eGFR leading to a change of at least 1 stage from baseline values, respectively.

Multivariate analyses using renal function as a time-varying covariate and with death unrelated to event as 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 Caravaggio 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 RI either moderate (eGFR lower than 60 ml per minute) or defined by eGFR lower than 50 ml per minute 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 at the cost of a not significant increase in clinically relevant non major bleeding. The efficacy to safety profile 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/1·73m^2); 15% had moderate RI and 1% to 2% had severe RI. [25] In the CLOT study, 24% of patients with 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 gynaecological 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 LMWHs and direct anti-Xa anticoagulants and potentially lead to anticoagulant overdosing and increase in bleeding complications. Whether dose reduction or dose adjustment of LMWH based on antiXa

activity are valid options to avoid increase in bleeding risk in patients with severe RI is uncertain. [28-29] The evidence in favor of these approaches is limited either in the general population of patients with VTE and in cancer patients with VTE. To date, the optimal anticoagulant agent and regimen in patients with severe renal failure is undefined. Among LMWHs, dalteparin seems to be associated with acceptable bleeding risk in patients with RI. [16,30-31] Among direct oral anti-Xa, dose reduction for patients with RI has been 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 and in cancer patients included in a randomized study that compared tinzaparin or dalteparin with warfarin. [12,15-16] These studies showed an increased risk for 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 already reported in the main Caravaggio study and we now add the 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 anticancer agents remains undefined. [32] Indeed, as these findings derive from subgroup analyses

and refer to limited numbers of events, 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 favourable 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 stage of eGFR. A previous study in patients with cancer-associated VTE reported on 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 DOACs vs. vitamin K antagonists (VKAs); 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] All 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. Patients 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 DOACs 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 can be preferred or, as an alternative, vitamin K antagonists can still be still an option. Despite 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 noninvasively estimate eGFR. eGFR is an accepted index of renal function, regardless of the formula used for calculation. The Cockcroft-Gault equation is at present the most widely used in clinical practice and was used in phase III clinical trials with DOACs to calculate eGFR and adjust the dose of the oral antiXa agents. For this reason, the Cockcroft-Gault equation is commonly used to adjust dosing of DOACs 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 DOACs. [35] All, Cockcroft–Gault, CKD-EPI and MDRD are serum creatinine-based estimations of eGFR and depends by age and gender. Differences across equations emerged in our study concerning proportions of patients classified with stage I or stage II RI between the Cockcroft-Gault and CKD-EPI equations. The majority of reclassification 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 Caravaggio were excluded from this analysis due to the lack of baseline creatinine value at time of inclusion or to the violation of the inclusion requirement of need for creatinine clearance greater than 30 ml per minute. The study has been 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 per minute), as these patients were excluded from Caravaggio study. Our study has the strength related to the 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 haves RI when diagnosed with VTE, or experience a deterioration of renal function in the six-month period beyond 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 bleedings seem more common in patients with moderate RI receiving apixaban in comparison to dalteparin.

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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

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			
Cockroft 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 Cockroft-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 mITT analysis set in each group.

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 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

Table 4. Frequency of study outcome events based on baseline eGFR calculated according to the Cockroft-Gault formula

	Major Bleeding			HR (95% CI)	p-value for interaction		Major Bleeding			HR (95% CI)	p-value for interaction
	Overall	Apixaban	Dalteparin				**Overall**	Apixaban	Dalteparin		
eGFR <60* **n/N (%)**	11/275 (4·0)	5/137 (3·6)	6/138 (4·3)	0·84 (0·26-2·71)	0·8819	**eGFR <50*** **n/N (%)**	7/150 (4·7)	3/68 (4·4)	4/82 (4·9)	0·85 (0·19-3·80)	0·9757
eGFR ≥60* **n/N (%)**	33/867 (3·8)	16/436 (3·7)	17/431 (3·9)	0·92 (0·47-1·83)		**eGFR ≥50*** **n/N (%)**	37/992 (3·7)	18/505 (3·6)	19/487 (3·9)	0·91 (0·48-1·73)	
HR (95% CI)	1·06 (0·53-2·11)	1·02 (0·37-2·79)	1·11 (0·43-2·83)			**HR (95% CI)**	1·26 (0·56-2·84)	1·24 (0·37-4·20)	1·28 (0·43-3·79)		
	Recurrent VTE			**HR (95% CI)**	p-value for interaction		**Recurrent VTE**			**HR (95% CI)**	p-value for interaction
	Overall	Apixaban	Dalteparin				**Overall**	Apixaban	Dalteparin		
eGFR <60* **n/N (%)**	14/275 (5·1)	3/137 (2·2)	11/138 (8·0)	0·27 (0·08-0·96)	0·1085	**eGFR <50*** **n/N (%)**	6/150 (4·0)	0/68 (0·0)	6/82 (7·3)	N.A.	N.A.
eGFR ≥60* **n/N (%)**	64/867 (7·4)	29/436 (6·7)	35/431 (8·1)	0·82 (0·50-1·33)		**eGFR ≥50*** **n/N (%)**	72/992 (7·3)	32/505 (6·3)	40/487 (8·2)	0·76 (0·48-1·22)	
HR (95% CI)	0·67 (0·38-1·20)	0·31 (0·09-1·03)	0·97 (0·50-1·91)			**HR (95% CI)**	0·53 (0·23-1·22)	N·A·	0·87 (0·37-2·04)		
	Recurrent VTE or major bleeding			**HR (95% CI)**	p-value for interaction		**Recurrent VTE or major bleeding**			**HR (95% CI)**	p-value for interaction
	Overall	Apixaban	Dalteparin				**Overall**	Apixaban	Dalteparin		
eGFR <60* **n/N (%)**	23/275 (8·4)	8/137 (5·8)	15/138 (10·9)	0·53 (0·23-1·24)	0·3675	**eGFR <50*** **n/N (%)**	12/150 (8·0)	3/68 (4·4)	9/82 (11·0)	0·39 (0·12-1·40)	0·2947
eGFR ≥60* **n/N (%)**	93/867 (10·7)	42/436 (9·6)	51/431 (11·8)	0·81 (0·54-1·21)		**eGFR ≥50*** **n/N (%)**	104/992 (10·5)	47/505 (9·3)	57/487 (11·7)	0·78 (0·53-1·15)	
HR (95% CI)	0·76 (0·48-1·21)	0·59 (0·27-1·26)	0·91 (0·51-1·61)			**HR (95% CI)**	0·74 (0·41-1·34)	0·45 (0·14-1·46)	0·92 (0·46-1·86)		

	Clinically relevant non major bleeding			HR	p-value for		Clinically relevant non major bleeding			HR	p-value for
	Overall	Apixaban	Dalteparin	**(95% CI)**	interaction		**Overall**	Apixaban	Dalteparin	**(95% CI)**	interaction
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	p-value for		**Major bleeding or CRNMB**			HR	p-value for
	Overall	Apixaban	Dalteparin	**(95% CI)**	interaction		**Overall**	Apixaban	Dalteparin	**(95% CI)**	interaction
eGFR <60*	36/275	23/137	13/138	1·83 (0·92-	0·2011	**eGFR <50***	18/150	8/68	10/82	0·96	0·5026
n/N (%)	(13·1)	(16·8)	(9·4)	3·62)		**n/N (%)**	(12·0)	(11·8)	(12·2)	(0·38-2·40)	
eGFR ≥60*	89/867	46/436	43/431	1·06 (0·70-		**eGFR ≥50***	107/992	61/505	46/487	1·29	
n/N (%)	(10·3)	(10·6)	(10·0)	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)	(0·67-2·68)		

* mL/min/1·73m2

Notes: All patients in mITT set with an available baseline value of eGFR are considered in this table. eGFR cut-off of 50 ml per minute was used in some phase III studies with direct oral anticoagulants.

The Hazard Ratios (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 Hazard Ratio 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 VTE and active cancer vs history of cancer as covariates.

n = number of patients with events. N = total number of patients in each category.

Table 5. Risk factors for major bleeding, recurrent VTE or clinically relevant non-major bleeding according to Cox model with time-varying covariate

		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		**HR**	**95%CI**		**p**
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		**HR**	**95%CI**		**P**
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		**HR**	**95%CI**		**P**
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

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

*eGFR included in the analyses as log-transformed eGFR (see methods section)

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.

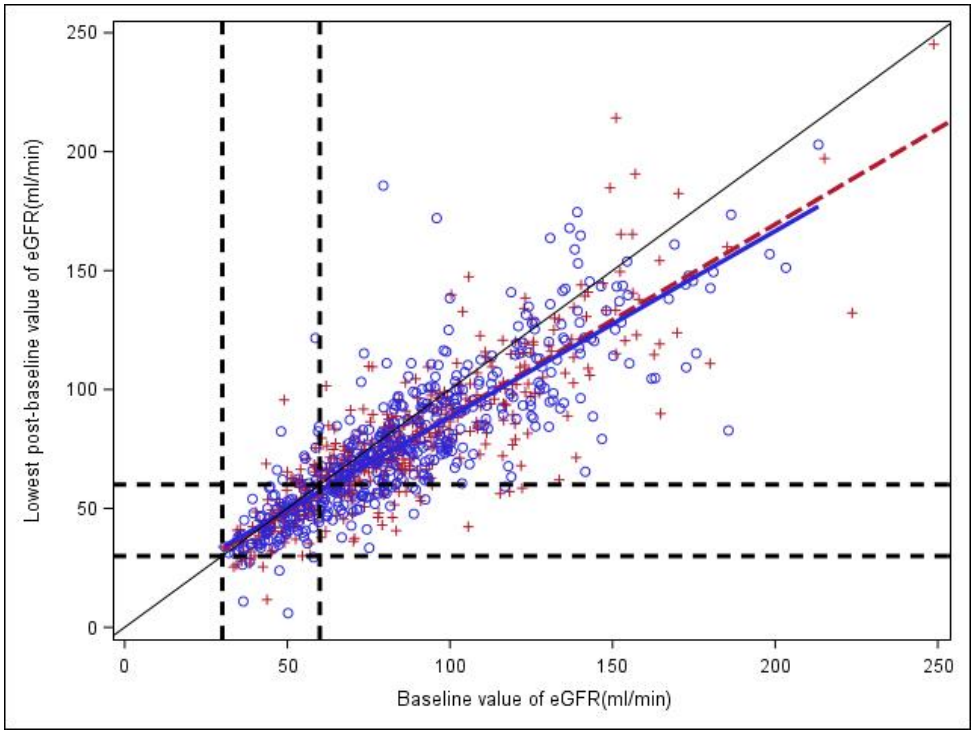
Missing values in eGFR post-baseline measurements were replaced using LOCF method.

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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