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Chronic kidney disease is associated with increased risk of venous thromboembolism recurrence

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ABSTRACT

Introduction: It is currently unclear whether chronic kidney disease (CKD) and the decrease in renal function can influence the risk of venous thromboembolism (VTE) recurrence.

Materials and methods: We performed an ambispective observational study on 409 patients with a previous episode of VTE. All the patients were included in the retrospective analysis whereas a subgroup of 260 individuals, without history of recurrence and that stopped oral anticoagulation, were then followed-up for a mean of 52.3 ± 20.7 months.

Results: At the enrollment, subjects with history of recurrent VTE were prevalently male with higher blood pressure and lower eGFR. Prevalence of CKD (defined as eGFR < 60 ml/min/1.73 m^2) was higher in patients with previous VTE recurrence with an adjusted OR of 5.69 (IC95% 2.17–14.90, p < 0.001) compared to patients with normal eGFR. Similar findings were obtained from the prospective study where an adjusted 5.32 HR for VTE recurrence was seen in patients with CKD compared to subjects with normal renal function (IC95% 1.49–18.95, p = 0.010). An increase in the risk of recurrent VTE was also observed in patients with mild decrease in renal function (eGFR 60–90 vs ≥ 90 ml/min/1.73 m^2 adjusted HR 2.84, IC95% 1.13–7.11, p = 0.025). Moreover, a multivariate Cox regression analysis including eGFR as continuous variable showed that renal function decrease was independently associated with the risk of VTE recurrence (p = 0.001).

Conclusions: CKD and mild decrease in renal function are associated with a significant increase in the risk of recurrent VTE.

1. Introduction

Despite significant improvements in both diagnosis and treatment of venous thromboembolic disorders, deep vein thrombosis (DVT) and pulmonary embolism (PE) still have a significant impact on mortality and morbidity in the general population [1,2]. A major challenge in the clinical management of patients affected by venous thromboembolism (VTE) is the prevention of recurrence. After a first thrombotic event, VTE recurrence has been observed in about 20–25% of patients after 5 years [3], and continues to increase over time, compromising almost 44% of patients after 20 years [4]. Moreover, recurrent venous thromboembolic events are associated with a significant mortality risk [5]. The optimal duration of anticoagulation therapy after the first DVT/PE event still remain a critical clinical decision, which is mainly based on the evaluation of the balance between the risk of thrombotic events and hemorrhagic complications [6]. Thus, the collection of reliable clinical data for the assessment of thrombotic risk represents a major determinant in the choice whether or not to prolong anticoagulant treatment over time. To date some clinical features, such as male gender, PE, proximal DVT, cancer, unprovoked events and residual vein thrombosis have been identified as strong predictors of VTE recurrence and are currently used in the clinical evaluation of patients affected by venous thrombosis [6]. Nevertheless, additional data are needed to better identify patients who require long-term anticoagulant therapy.

Current international guidelines and consensus define chronic kidney disease (CKD) as abnormalities of kidney structure or function (glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2) for > 3

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months. This degree of reduction in kidney function is now recognized as a strong predictor of future cardiovascular (CV) events [7]. The association between adverse CV outcome and CKD is independent from the role of traditional atherosclerotic risk factors and has been partly attributed to the generation of a procoagulant state [8,9]. Nevertheless, only a limited number of studies have specifically investigated the link between CKD and the risk of venous thrombotic events. In this field, some recent clinical investigations and meta-analyses performed in the general population suggested that CKD as well as mild decrease in renal function are independently associated with an increased risk of a first VTE event [10–13]. However, no specific investigations have been performed in patients with a previous VTE to establish whether decreased renal function might also be associated with higher risk of thrombotic recurrence. To investigate this possibility we performed an ambispective cohort study on a population of patients with previous VTE events. In particular, we studied the association between different degrees of renal function decrease and the risk of VTE recurrence.

2. Materials and methods

2.1. Population and study design

We performed an ambispective observational cohort study on 409 patients who were referred between October 2010 and October 2016 to the Thrombosis Unit of the Cà Foncello University Hospital in Treviso and had a previous diagnosed episode of DVT and/or PE. All the clinical characteristics of the index VTE event were obtained from the medical record of the patients. In particular, for each subject the DVT diagnosis was obtained through complete lower limb compression ultrasonography (CUS) and was based on the observation of incomplete compressibility of the vein, including the distal veins. Diagnosis of PE was confirmed by computed tomographic (CT) angiography or ventilation-perfusion scintigraphy (V/Q scan). The latter was considered diagnostic in case of mismatched segmental perfusion defects whereas CT scans were considered diagnostic for PE in case of perfusion defects observed either in the segmental or proximal pulmonary vessels. At the time of diagnosis each patient was hospitalized and treated with either intravenous adjusted-dose of unfractioned heparin or fixed dose low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKA) for at least three months (decision to prolong the oral anticoagulation was made on individual basis considering the risk of recurrent VTE). All the VTE events without evidence of triggering conditions were denoted as “unprovoked”, whereas we considered as “provoked VTE” the events associated with the following conditions: surgery, trauma, bone fracture, immobilization, acute medical disease, oral contraceptives, hormonal replacement therapy, or pregnancy. In the present study, we did not include patients with active or previous cancer and those with VTE diagnosis < 3 months apart from the enrollment visit. In particular, we collected information about the type of VTE (unprovoked or provoked) the site of DVT (proximal or distal), presence of PE, history of recurrence, and presence of thrombophilia. Results of screening for thrombophilic conditions were available for 308 patients and included: anti-thrombin III (n = 5), factor V Leiden mutation (n = 44), prothrombin G20210A mutation (n = 40), protein C (n = 10) and protein S (n = 16) deficiency, lupus anticoagulant (n = 7). The average temporal distance between the VTE event and the enrollment in the study was 60.6 months (range 4–179 months).

The prospective study was then performed in the same population focusing on the subgroup of patients without history of VTE recurrence and not taking oral anticoagulants at enrollment (n = 228). We also considered for the prospective analysis all the subjects that stopped anticoagulants during the clinical follow-up (n = 37). In this case the follow-up time was initiated at the time of the interruption of the therapy. A total of 265 subjects fulfilled these criteria and each patient was contacted through telephonic interview to obtain information about the occurrence of the following clinical events: VTE recurrence (DVT and/or PE), acute coronary syndrome (ACS), stroke/transient ischemic attack (TIA), death. All clinical data reported by the patients (or by the relatives) were verified through direct examination of the medical records. Clinical information was not retrieved for 5 subjects, thus the final prospective analysis was performed on a total of 260 patients (for a detailed flow-chart see the figure in supplemental material).

The study has been carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association and was approved by the local Ethic Committee. All the subjects enrolled gave written informed consent.

2.2. Clinical data collection and biochemical analysis

Data collected from each patient were: age, sex, height, weight, body mass index (BMI, calculated as body weight (kg) divided by the square of the height (m)), history of atherosclerotic cerebro-cardiovascular events (ischemic stroke, TIA, ACS), known diabetes, current use of antihypertensive drugs, oral anticoagulants, antiplatelet drugs and lipid lowering treatment. Blood pressure (BP) was measured in sitting position and after 5 min of rest by using a mercury sphygmomanometer of adequate cuff size. The mean of three measures 1 min apart was considered to establish systolic BP (SBP) and diastolic BP (DBP) values. All the subjects underwent fasting blood sampling to measure creatinine level and GFR was estimated through the 2009 CKD-EPI creatinine equation. CKD stage of each subject was established by using GFR categories as indicated by KIDGO guidelines. In particular CKD staging was performed as follow: stage 1: GFR ≥ 90 ml/min/1.73 m^2, stage 2: 60–89 ml/min/1.73 m^2, stage 3: 59–30 ml/min/1.73 m^2, stage 4: 30–15 ml/min/1.73 m^2, stage 5: < 15 ml/min/1.73 m^2.

2.3. Statistical analysis

Data are expressed as mean ± standard deviation (SD) or as percentage, where appropriate. In the analysis of baseline data comparison between groups for continuous variables was performed by using Student's *t*-test for normally distributed parameters and Mann-Whitney *U* test for variables without normal distribution (Shapiro Wilks test was used to test the normality of distribution of continuous variables). Chi-square test was used for comparison of categorical variables. A binary logistic regression analysis was performed to estimate univariate and multivariate odds ratios (OR) and 95% confidence intervals (CI) for VTE recurrence in patients with CKD.

In the prospective study, univariate and multivariate Cox proportional hazards models were used to estimate the association of different CKD stages with the risk of recurrent VTE. Adjustment was made taking into account gender, age, BMI at the enrollment as well as the characteristics of the index event (type of VTE and DVT site). An additional multivariate analysis was performed considering eGFR as continuous variable.

Statistical significance was considered as a two-tailed $p < 0.05$. All the analyses were performed using PAWS statistics 18.0 (SPSS Inc. Chicago IL, USA).

3. Results

3.1. Population characteristics and baseline data

We enrolled a total of 409 subjects with previous objectively documented VTE (DVT and/or PE). In this population we identified a group of 73 (17.8%) individuals, who also experienced at least one episode of VTE recurrence. Differences in demographic and laboratory characteristics between subjects with or without history of recurrence are summarized in Table 1. In particular, patients with recurrent VTE were prevalently male (65.8% vs 53%, p = 0.046) with higher SBP

Table 1
Population characteristics.

	History of recurrent VTE	No history of recurrence	p
N	73	336	
Mean age, years (SD)	60.9 (12.9)	57.9 (14.8)	ns (0.10)
Male sex, n (%)	48 (65.8)	178 (53)	0.046
BMI (SD)	28.4 (4.5)	27.2 (4.7)	ns (0.050)
Mean SBP, mmHg (SD)	140.5 (17.8)	134 (19.8)	0.010
Mean DBP, mmHg (SD)	89.2 (10.5)	86.7 (11)	ns (0.08)
Mean eGFR, ml/min/1.73 m^2 (SD)	77.4 (21.6)	87 (18.4)	0.001
History of atherosclerotic events, n (%)	4 (5.6)	30 (8.9)	ns (0.35)
Diabetes, n (%)	9 (12.3)	30 (8.9)	ns (0.36)
Therapy with statins, n (%)	11 (15.1)	57 (16.9)	ns (0.70)
Antiplatelet therapy, n (%)	2 (2.7)	40 (11.8)	0.020
Oral anticoagulants, n (%)	56 (76.7)	113 (33.6)	< 0.001
CKD stages			
CKD 1, n (%)	22 (30.1)	150 (44.6)	
CKD 2, n (%)	34 (46.6)	165 (49.1)	
CKD 3, n (%)	16 (21.9)	17 (5.1)	
CKD 4, n (%)	1 (1.4)	3 (0.9)	
CKD 5, n (%)	0	1 (0.3)	
VTE characteristics (first event)			
Type of VTE, unprovoked (%)	41 (56.9)	191 (56.8)	ns (0.98)
DVT site, proximal (%)	60 (87)	190 (69.1)	0.003
Thrombophilic defect, yes (%)*	33 (56.9)	107 (42.8)	ns (0.052)
Pulmonary embolism, yes (%)	10 (13.9)	117 (34.8)	< 0.001
Pregnancy/estroprogestin, yes (%)	4 (6)	46 (13.7)	ns (0.055)

* Data available for 308 patients.

levels (140.5 ± 17.8 vs 134 ± 19.8, p = 0.010) and trend to increased BMI (28.4 ± 4.5 vs 27.2 ± 4.7, p = 0.050). No differences between the two groups were found in term of mean age, prevalence of diabetes, history of atherosclerotic events as well as therapy with statins. As expected, a higher number of subjects undergoing VKA treatment was found in the VTE recurrence group (76.7% vs 33.6%, p < 0.001). On the contrary the use of anti-platelet agents was more prevalent in patients without recurrent VTE (11.8% vs 2.7%, p = 0.020). As for the characteristics of the initial event, patients with history of recurrence showed significantly higher prevalence of proximal DVT (87% vs 69.1%, p = 0.003) and lower number of PE (13.9% vs 34.8%, p < 0.001). Individuals with recurrence also had higher prevalence of thrombophilia and a lower number of events associated with pregnancy/hormone replacement therapy, although these differences did not reach the statistical significance. The two groups showed similar prevalence of unprovoked/provoked VTE events. All values are shown in Table 1.

Creatinine blood levels were measured in each patient at the enrollment and used to estimate GFR (eGFR) by using the 2009 CKD-EPI creatinine equation. Each subject was then assigned to a CKD stage on the basis of eGFR values. We found that patients with history of recurrence had significantly lower mean eGFR levels as compared to subjects without recurrent VTE (77.4 ± 21.6 vs 87 ± 18.4, ml/min/1.73 m^2, p = 0.001). In Table 1 we have also summarized the distribution of patients according to the CKD stages. In particular, the prevalence of stage ≥ 3 CKD (eGFR < 60 ml/min/1.73 m^2) was significantly higher in patients with recurrent VTE. We found that 23.3% of patients with history of recurrence had CKD, whereas only 6.3% of those without recurrent VTE belonged to CKD stage ≥ 3 (p < 0.001). These differences translated into an OR for VTE recurrence of 5.51 (95%IC, 2.52–12.04, p < 0.001) when comparing CKD patients with subjects with normal renal function (CKD stage 1, eGFR ≥ 90 ml/min/1.73 m^2) (Table 2). These findings remained significant even after adjustment for age, gender, BMI, type of VTE and site of DVT with an adjusted OR for recurrence of 5.69 (95% IC 2.17–14.90, p < 0.001) among subjects with CKD (Table 2). A non-significant trend of increased risk in VTE recurrence was also found in patients with mild decrease in renal function (CKD stage 2, 60–89 ml/min/1.73 m^2).

Table 2
Odds ratios for VTE recurrence according to CKD stages (baseline analysis).

CKD stage	Crude OR (95% CI)	p	Adjusted OR (95% CI)*	p
CKD 1	Reference		Reference	
CKD 2	1.40 (0.78–2.50)	0.25	1.41 (0.71–2.82)	0.32
CKD ≥ 3	5.51 (2.52–12.04)	< 0.001	5.69 (2.17–14.90)	< 0.001

* Adjusted for age, gender, BMI, type of VTE, DVT site.

3.2. Prospective study

The longitudinal clinical follow-up was performed in 260 patients without history of recurrence and not taking oral anticoagulants at enrollment visit. This cohort also includes 37 patients who stopped oral anticoagulation during the study. In this case the follow-up time was initiated at the time of therapy interruption. The patients were followed for an average time of 52.3 ± 20.7 months (range 1–78 months) and during this time period 34 subjects (9.4%) had symptomatic recurrence of VTE. The recurrence was ipsilateral DVT in 20 patients, contralateral DVT in 9 cases, PE in 5 subjects and in 10 cases was a combination of DVT/PE. Twenty-five subjects (73%) had an unprovoked recurrence, whereas in 9 cases the recurrent event was considered as "provoked" (4 patients with traumatic/bone fracture events and 5 cases with the recurrence observed during hospitalization for medical conditions). Seven patients died during the clinical follow-up and in 3 cases the death was ascribed to fatal PE. When we looked at baseline eGFR values of the 34 patients with VTE recurrence we found that 9 patients (26.5%) had normal renal function, 20 patients (58.8%) showed mild decrease in eGFR (CKD stage 2) and 5 patients (14.7%) had CKD (see supplemental Table 1). The latter represented 13.1% of the patients assigned to CKD stage ≥ 3 at the baseline, and led in our cohort to a total of 57.8% of the patients with CKD that experienced at least one episode of VTE recurrence. Cox regression analysis was then performed to estimate crude and adjusted HR for VTE recurrence on the basis of baseline renal function. Of interest, our data indicated that even patients with mild decrease in renal function (CKD stage 2) had a significant increase in the risk of VTE recurrence as compared to subjects with normal eGFR (CKD stage 1)(Table 3). Nevertheless, the highest HRs values were seen when comparing the rate of VTE recurrence between patients with CKD and subjects with normal renal function (HR 4.58, 95%IC 1.53–13.68, p = 0.006), a finding that remained significant even after adjustment for age, gender, BMI, type of VTE and DVT site (HR 5.32, 95%IC 1.49–18.95, p = 0.010). Fig. 1 shows the cumulative risk of VTE recurrence observed in these three categories of patients. In particular, the worst clinical outcome was observed in patients with baseline eGFR values below 60 ml/min/1.73 m^2, whereas patients belonging to CKD stage 2 showed an intermediate risk profile between patients with CKD

Table 3
Hazard ratios for VTE recurrence according to CKD stages (prospective study).

CKD stage	Crude HR (95% CI)	p	Adjusted HR (95% CI)*	p
CKD 1	Reference		Reference	
CKD 2	2.58 (1.17–5.68)	0.018	2.84 (1.13–7.11)	0.025
CKD ≥ 3	4.58 (1.53–13.68)	0.006	5.32 (1.49–18.95)	0.010
CKD 1	Reference		Reference	
CKD ≥ 2	2.47 (1.15–5.30)	0.020	2.47 (0.99–6.13)	0.051

* Adjusted for age, gender, BMI, type of VTE, DVT site.

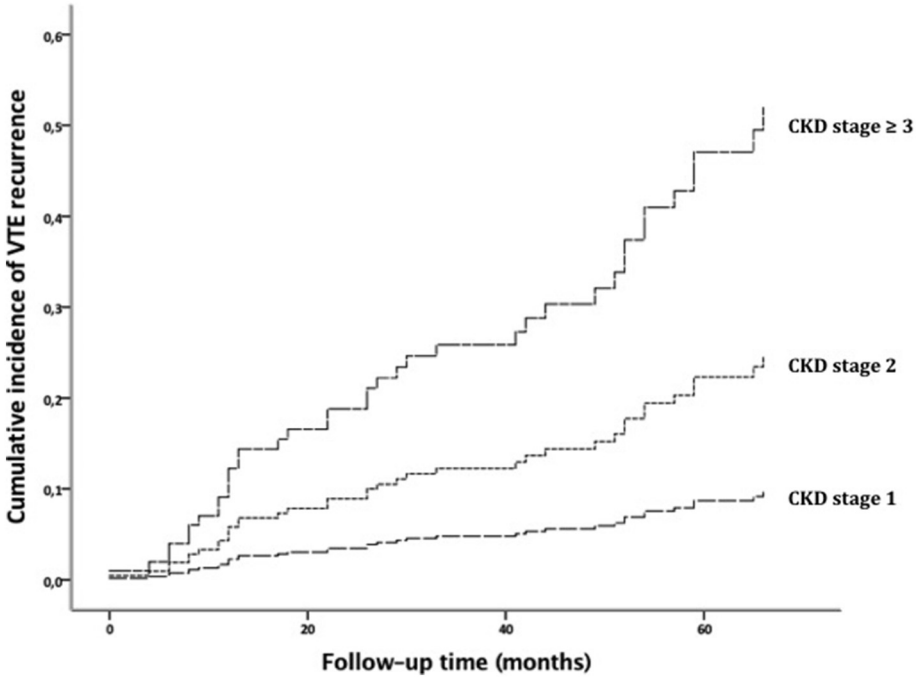

Fig. 1. Cumulative incidence of VTE recurrence according to CKD stage.

and those with normal baseline renal function. In Table 2 we also reported the HRs for VTE recurrence obtained comparing patients with normal renal function with subjects with GFR < 90 ml/min/1.73 m^2 (CKD stage = 1 vs CKD stage ≥ 2). In particular, patients assigned to CKD stage ≥ 2 showed an HR of 2.47 (95%IC 1.15–5.30, p = 0.020) for VTE recurrence as compared to subjects with normal renal function, a finding that remain close to significance after adjustment (HR 2.47, 95%IC 0.99–6.13, p = 0.051). A multivariate Cox regression analysis was also performed including eGFR as continuous variable. This model, which again included age, gender, BMI, type of VTE and DVT site, showed that only decrease of eGFR was significantly associated with the risk of VTE recurrence (p = 0.001). In particular, we observed that for each additional unit of eGFR the hazard of recurrence decreases by 4%, whereas for each 10 ml/min/1.73 m^2 increase in eGFR the hazard decreases by 34% (see supplementary Table 2).

4. Discussion

In the present study, we demonstrated that among patients with a previous episode of DVT and/or PE the presence of CKD is associated with a significant increase in the risk of VTE recurrence. In our cohort, both the analysis of baseline and prospective data have clearly indicated that subjects with CKD carry a higher risk of venous thrombosis recurrence as compared to patients with normal renal function. When we looked retrospectively at the association between the presence of CKD and the history of VTE recurrence we found that the prevalence of subjects with GFR below 60 ml/min/1.73 m^2 was significantly higher among patients with recurrent VTE (23.3% vs 6.3%) with an adjusted OR of 5.69. These baseline data were then confirmed by the follow-up study, which indicated that patients with CKD at baseline had about a five-fold increase in the risk of venous disease recurrence as compared to patients with normal eGFR. Of note, the prospective study also showed that a considerable increase in the risk of VTE recurrence could be found even in patients with only mild impairment in renal function. In fact, compared to patients in CKD stage 1, subjects belonging to CKD stage 2 (GFR between 60 and 89 ml/min/1.73 m^2) displayed an adjusted 2.84 HR of recurrence (Fig. 1 and Table 3). Moreover, when compared to those with normal renal function, patients with eGFR < 90 ml/min/1.73 m^2 showed a 2.4-fold increase in the risk of recurrent VTE.

As far as we know, this is the first study that specifically investigated the impact of renal function on the risk of recurrent VTE. Nevertheless, our findings are in line with previous data collected in general population cohorts, where the risk of a first VTE episode was found to be significantly higher among patients with CKD [11–13]. Moreover, in agreement with our data, these population studies highlighted the presence of a sizable increase in the risk of venous disease even among patients in the non-CKD range of GFR. For instance, the LITE study showed that the risk of incident VTE gradually began to increase with GFR as high as 75 ml/min/1.73 m^2 [11]. These previous investigations also demonstrated that the association between CKD and VTE risk was evident for both provoked and unprovoked events and was not dependent from the etiology of kidney disease [12]. Despite this evidence collected in the general population, so far no specific investigation has been performed to elucidate the impact of kidney disease on VTE recurrence after a first episode of venous thrombosis. The only data available on this topic arise from the PREVEND study that investigated the association between the presence of microalbuminuria (≥ 20 mg/l) and the risk of VTE recurrence [14]. This study was performed in 351 patients with a previous thrombotic event and showed a significant adjusted HR of 1.95 for recurrent VTE in patients with microalbuminuria. Unfortunately, this previous study did not include information about serum creatinine or GFR and for this reason the findings cannot be directly compared to our data. Nevertheless, these two longitudinal investigations have clearly indicated that the presence of impaired renal function is a strong predictor of the future risk of VTE recurrence.

There is no definitive pathophysiological justification to explain the strong association between the risk of VTE recurrence and the decrease in renal function observed in our study. A number of studies clearly showed that end-stage kidney disease (ESKD) is associated with a systemic pro-inflammatory status that favors the acceleration of endothelial dysfunction and vascular damage [15]. Indeed, some of the pathological noxae identified in ESKD, such as oxidative stress, increased circulating levels of inflammatory mediators, accumulation of ADMA, deregulation in calcium-phosphate homeostasis, are known to cause arterial disease progression and may also induce endothelial injury in the venous system. As yet, no data are available to support this

possibility and additional studies on this topic are warranted. Presence of overt proteinuria and nephrotic syndrome are clinical conditions associated with significant risk of VTE mainly because of renal loss of anti-thrombotic factors [16]. Nevertheless, some studies indicated that even the presence of mild-to-moderate decrease in renal function is accompanied by the development of a procoagulant state [17]. Circulating levels of procoagulant factors, such as fibrinogen, factor VII, plasmin-antiplasmin complex, von Willebrand factor, D-dimers, circulating microparticles [9,18–20] are increased in patients with reduced renal function, suggesting the generation of a prothrombotic milieu that might influence the risk of recurrent VTE. This hypothesis is further supported by other evidence showing that even platelet reactivity is increased in patients with CKD [21] a phenomenon also seen in patients with different comorbidities that are known to increase the risk of thrombotic events [22].

Indeed, our findings can have important practical implication in the clinical management of patients affected by VTE. As mentioned above, the decision whether or not to prolong anticoagulant therapy after a first episode of VTE is a critical step in the management of patients with venous thrombosis. Some scores, such as the DASH prediction score [23] and the Vienna prediction model [24], have been developed to estimate the risk of VTE recurrence and to support physicians in the management of patients with VTE. These models are based on the identification of known predictors of VTE recurrence, in particular D-dimer levels, male gender, proximal DVT, use of estrogens. Other clinical features, such as obesity, cancer, residual vein thrombosis and strong thrombophilic defects are currently used on individual basis to establish the need for prolonged anticoagulant therapy. However, a certain degree of uncertainty still remains in the clinical approach to some group of patients with VTE. Our data indicate that independently from age, gender, BMI, and VTE characteristics the presence of CKD (GFR $<$ 60 ml/min/1.73 m^2) is strongly associated with the risk of recurrent VTE. Hence, it appears that the estimate of GFR might represent a simple, but highly predictive clinical tool to use in the management of patients with a first episode of venous thrombosis. Present findings need to be confirmed by other investigations but the coherence between our retrospective and prospective data and the similarity with data coming from general population studies [10,11], strongly suggest that CKD presents a solid risk factor for the first VTE event as well as for the risk of thrombosis recurrence. Additional investigations should be also aimed at describing the potential interplay between the decrease in renal function and the persistence of residual vein thrombosis as well as the interaction with D-dimer levels, that have been already shown to be increased in patients with CKD [20].

We acknowledge that the present report has some limitations. First, in our population, a heterogeneous temporal distance exists between the last episode of VTE and the recruitment in the study. Moreover, we did not collect information on albuminuria and for this reason we cannot fully compare our results with those obtained in the general population or in the PREVEND study [14]. Nevertheless, previous studies in the general population indicated that the association of microalbuminuria with VTE risk was evident across most GFR categories and that the lower GFR and the higher albumin-to-creatinine ratio (ACR) categories did not show multiplicative effects on VTE risk [10]. On this basis we believe that the interpretation of our data is not significantly hampered by the lack of data about ACR values.

In conclusion, we showed that the presence of CKD defined as GFR $<$ 60 ml/min/1.73 m^2 was associated with a significant increase in the risk of VTE recurrence. This independent association was also observed in patients with only mild decrease in renal function and can have relevant impact in the clinical course of patients with a first episode of venous thrombosis. Additional studies are needed to establish whether CKD should be definitively added to the list of predictors of VTE recurrence.

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Conflict of interest statement

All the authors declared no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2017.10.011.

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