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Full Length Article

Very elderly patients with venous thromboembolism on oral anticoagulation with VKAs or DOACs: Results from the prospective multicenter START2-Register Study

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ABSTRACT

Introduction: Few data are available on the safety of anticoagulation in very elderly patients treated with Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) for venous thromboembolism (VTE).
Methods: We carried out a prospective cohort study on VTE patients aged ≥85 years enrolled in the Survey on anticoagulaTed pAtients RegisTer (START2-Register) on treatment with VKAs or DOACs, with the aim to evaluate mortality, bleeding and thrombotic rates (venous and arterial).
Results: We enrolled 272 patients, 58.7% on VKA and 41.3% on DOACs. Baseline characteristics were similar between treatment groups, with a higher prevalence of renal failure in VKAs patients and of a history of bleeding and previous stroke/TIA in DOACs patients. During follow-up of 429 patient-years, 15 major and non-major clinically relevant bleedings were recorded (rate 3.5 × 100 pt-yrs), 5 were major bleeds (rate 1.2 × 100 pt-yrs), 1 in a patient on aspirin (rate 4.3 × 100 pt-yrs). Bleeding rate was higher in patients on DOACs (crude HR 4.7; 95%CI 1.5–15.01). Eight thrombotic events were recorded (rate 1.9 × 100 pt-yrs), 3 recurrent VTE and 5 stroke/TIA. Overall, the incidence of thrombotic events was higher in DOACs patients (crude HR 4.5; 95% CI 1.5; 13.3). The rate of recurrent VTE was similar in the two group. Mortality rate was significantly lower in DOACs patients (crude HR 0.30; 95% CI 0.1;0.9).
Conclusion: A higher bleeding risk was found in very elderly VTE patients on DOACs despite the wide use of low-dosages. Similarly a higher thrombotic risk was found while the incidence of recurrent VTE was low and similar between the groups. Mortality rate were significantly lower in DOACs patients.

1. Introduction

The term "venous thromboembolism" (VTE) includes deep vein thrombosis (DVT) of the lower limbs and/or pulmonary embolism (PE). VTE is a common disease, especially in the elderly, and is associated with increased risk of mortality, hospitalization and chronic complications such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension. A first episode of VTE confers a higher risk for recurrences, therefore VTE must be considered a chronic disease.

Oral anticoagulation either with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) has a proven efficacy in the short and long-term prevention of VTE recurrences. However, the long-term safety of anticoagulant treatment remains a matter of concern, in particular for elderly patients. No randomized-controlled trials (RCTs) of

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DOACs versus VKA were specifically designed to address this issue in a population of elderly patients. A meta-analysis of clinical trials showed that in patients aged 75 years or more, DOACs were more effective in reducing VTE recurrences and safer than warfarin [1,2]. However, in these RCTs elderly patients represented only about 12–15% of the whole study populations, with the exception of the Recover II study (20%) and the Resonate study (30%) [3].

Therefore, additional evidence is needed on the safety and effectiveness of oral anticoagulant therapy (VKAs or DOACs) in very elderly patients with acute VTE and for those who require extended treatment. Moreover, it is worth collecting data from real-world patients about the use of low-dose DOACs in this setting.

We have carried out a multicenter, prospective cohort study on patients aged ≥85 years with a VTE event enrolled in the Survey on anticoagulaTed pAtients RegisTer (START2-Register) who started a treatment with either VKAs or DOACs to evaluate the type and duration of anticoagulant therapy and the incidence of adverse events.

2. Methods

The START2-Register is an observational, multicenter, prospective cohort study that includes adults (> 18 years) who start anticoagulation therapy, whatever the clinical indication for the therapy, the drug and dosage used [4]. The aim of the START2-Register is to collect data on effectiveness and safety of anticoagulant treatments, on determinants of adverse events in anticoagulated patients, as well as on their quality of life and compliance to treatment. The registry has been approved on October 2011 (N = 142/2010/0/0ss) by the Ethical Committee of the Institution of the Coordinating Member (AziendaOspedaliero-Universitaria, Policlinico S. Orsola-Malpighi, Bologna, Italy), all patients gave their written informed consent before enrollment. The study is registered in ClinicalTrials.gov Identifier: NCT02219984; it is ongoing and actively recruiting. Here we present the results of the cohort of patients with venous thromboembolism (VTE) who started the anticoagulation at the age ≥85 years. For the purpose of the present analysis, data were collected from January 2012 to April 2018. VTE events are considered as unprovoked if they are not temporally associated with a major risk factor within 3 months of diagnosis (surgery with general or spinal anesthesia, lower limb fracture, casting or no weight bearing for ≥3 days, bed-bound for 3 days due to acute illness), or are associated with a minor risk factor [5].

All participating centers are asked to consecutively include patients who start anticoagulant treatment, for any indication and with any available drug, if this is planned to last for at least 3 months. Patients with life-expectancy < 6 months, or not residents in the participant region, or planning to leave in the next six months after enrolment are not eligible, as well as patients already enrolled in phase II or III clinical studies. Patients were followed-up during anticoagulant treatment, and follow-up was stopped when the treatment was withdrawn. Participants are required to enroll their patients consecutively, without any a priori exclusion criteria other than life-expectancy or geographical inaccessibility. Definition of the time-frame for enrolment (e. g. one week every month, or the first month of the year) is left at each participant's discretion, as long as it provides a random enrolment of patients. Baseline patient's clinical features are recorded by participants on web-based case report forms (CRF) and include: demographic and clinical characteristics of patients, clinical indication for treatment, associated risk factors for thromboembolic complications or bleeding occurring during treatment, laboratory routine data, type of anticoagulant drug used and dose (or expected therapeutic range), use of concomitant drugs. For patients treated with VKA, all INR controls, the subsequent dosing prescriptions and information at each visit about possible clinical events and changes in the medical history are automatically captured via informatics. All INRs were recorded and time in therapeutic range (TTR) [6] of the last 6 months of treatment was reported. Participants are required to regularly follow-up all enrolled patients at least quarterly, by phone call or ambulatory visit. An ambulatory follow-up visit is mandatory at least annually. In the presence of severe dementia or frequent falls or bed rest the patients were defined frail. Creatinine clearance was calculated by the Cockroft-Gault formula [7]. Patients are stratified for baseline bleeding risk evaluation according to HAS-BLED score [8].

Major endpoints of the study were bleeding events, VTE recurrence, and death for all causes. Major bleeding (MB) were defined as recommended by the International Society on Thrombosis and Haemostasis [9]. Clinically relevant non-major bleeding (CRNMB) are defined as any overt bleeding requiring a medical intervention (hospitalization, surgery or interventional procedure, further diagnostic imaging, laboratory test or specialist evaluation) and/or treatment discontinuation, and not meeting any of the criteria for major bleeding [10].

Thromboembolic complications, such as new or recurrent DVT or PE episodes, stroke, transient ischemic attack (TIA), peripheral embolism, and acute myocardial infarction (AMI) are recorded. If not specified differently in relation to specific study designs, thrombotic complications are adjudicated by the local investigators, based on clinical signs and symptoms combined with objectively confirmed diagnostic radiology and laboratory tests (color-Doppler ultrasound investigation, magnetic resonance imaging, computed tomography, electrocardiography, laboratory markers). Death for all causes were considered; in particular death was defined as consequence of bleeding or of thrombotic events or not related to anticoagulation in all the other cases.

2.1. Statistical analysis

Data were described as the mean value and standard deviation (SD) for continuous variables and proportions for categorical variables. Differences between continuous values were assessed using the unpaired *t*-test, categorical variables were compared by the Chi-square test or Fisher exact test as appropriate.

The median and interquartile range (IQR) follow-up time were calculated and the median test applied to test difference between groups.

The incidences of death, thrombotic accidents, and bleeding events were calculated by dividing the number of events by person time at risk. The incidence rate ratio and together with the 95% confidence interval (95%CI) were calculated.

The crude hazard ratios (HRs) with the 95%CI, and a multivariate hazard model was calculated for the three outcomes. All analysis was carried out using SAS statistical package (Version 9.4 for Windows. SAS Institute Inc. Cary NC).

3. Results

The present study analyzed 272 patients who started anticoagulation at the age ≥85 years, and who were included in the START2-Register during the interval time February 2012–April 2018 for the occurrence of a VTE episode. The baseline characteristics of the whole population are detailed in Table 1. The mean age of patients was 88.1 years, and patients on DOACs were significantly older than patients on VKAs. Sixty-nine patients (25.4%) were aged ≥90 years at the beginning of treatment. Patients were followed for a total period of 429 patient-years; 7 (2.6%) patients were lost at follow-up, 52 (19.0%) patients stopped treatment after the established period of treatment, 12 (4.4%) stopped treatment for the onset of a contraindication; 32 (11.7%) patients still on treatment were no longer followed by the participating centre.

The anticoagulant treatment was warfarin in 156 patients (57.3%) and direct oral anticoagulants (DOACs) in 116 patients (42.7%), and 15 patients (5.5%) were also on treatment with antiplatelet drugs (9 with low-dose aspirin, and 6 with clopidogrel), as reported in Table 2.

Table 1
Clinical characteristics of patients.

	All patients (N = 272)	VKA (N = 156)	DOACs (N = 116; naive 93, 80.2%)	p Value
	N%	N%	N%	
Sex- female	178 (65.4)	99 (63.5)	79 (68.1)	0.4
Age (years) - mean (SD)	88.1 (3.0)	87.6 (2.3)	88.8 (3.7)	0.001
Weight < 60 kg	65 (23.9)	42 (26.9)	23 (19.8)	0.17
Follow-up (years)	429	312	117	
Mean follow-up (months) (SD)	19.1 (16.8)	24.3 (19.0)	12.2 (9.6)	0.01
Co-morbidity				
Creatinine clearance < 30 mL/min	34 (12.5)	28 (17.9)	6 (5.2)	0.001
Creatinine clearance 30–50 mL/min	150 (55.1)	83 (53.2)	67 (57.8)	0.46
Hemoglobin < 10 g/dL	12 (4.7)	7 (4.5)	5 (4.3)	1.0
Platelet count < 100,000	3 (1.1)	2 (1.3)	1 (0.9)	1.0
Chronic disease	16 (5.9)	10 (6.4)	6 (5.2)	0.8
Active cancer	11 (4.0)	9 (5.8)	2 (1.7)	0.2
Diabetes mellitus	36 (13.0)	16 (10.3)	20 (17.2)	0.1
Hypertension	191 (70.2)	114 (73.1)	77 (66.4)	0.2
Previous stroke/TIA	27 (9.9)	10 (6.4)	17 (14.7)	0.04
Previous bleeding	11 (4.0)	3 (1.9)	8 (6.9)	0.06
Coronary artery disease	29 (10.7)	19 (12.2)	10 (8.6)	0.4
Heart failure	18 (6.6)	11 (7.1)	7 (6.0)	0.8
POAD	18 (6.6)	9 (5.8)	9 (7.8)	0.6
COPD	38 (14.0)	24 (15.4)	14 (12.1)	0.5
Frail subjects[a]	50 (18.4)	31 (19.9)	19 (16.4)	0.5
Bleeding risk stratification scores				
HASBLED - mean (SD)	2.0 (0.7)	2.05 (0.7)	2.0 (0.8)	NS

[a] Patient with dementia or bed rest or prone to fall.

Table 2
Type of treatment and co-medications.

	All patients (N = 272)	VKA (N = 156)	DOACs (N = 116)	p Value
	N%	N%	N%	
Type of anticoagulant drug				
Warfarin		156 (100)		
Apixaban			43 (37.1)	
Dabigatran			5 (4.3)	
Edoxaban			7 (6.0)	
Rivaroxaban			61 (52.6)	
Low-dose DOACs			52 (44.8)	
Co-medications				
Antiplatelet drugs	15 (5.5)	9 (5.8)	6 (5.2)	1.0
Proton pump inhibitor	127 (46.7)	79 (50.6)	48 (41.4)	0.8
Statins	43 (15.8)	19 (12.2)	24 (20.7)	0.1
Psychotropic drugs	48 (17.6)	30 (19.2)	18 (15.5)	0.6

Among DAOC patients 93, (80.2%) were naïve to treatment. Patients on warfarin showed a median time in therapeutic range (TTR) of 68% (interquartile range 54–79%); 52/116 (44.8%) patients on DOACs were on treatment with the low dosage available for the treatment of acute VTE for each drug.

The prevalence of patients with severe renal failure (creatinine clearance < 30 mL/min) was significantly higher in patients on warfarin with respect to patients on DOACs. Conversely, the prevalence of history of stroke/TIA and history of bleeding was significantly higher in DOACs patients (Table 1). All other clinical characteristics were similar between patients on warfarin and patients on DOACs (Table 1). Concomitant use of antiplatelet agents was also similar between the 2 treatment groups (Table 2).

The index event was deep vein thrombosis (DVT) in 148 patients (54.4%), and VTE was unprovoked in 217 patients (79.8%), with a similar distribution between patients on warfarin and patients on DOACs (Table 3).

Table 3
Characteristics of VTE index event.

	All patients (N = 272)	VKA (N = 156)	DOACs (N = 116)	p Value
	N%	N%	N%	
Site of index event				
DVT	148 (54.4)	82 (52.6)	66 (56.9)	0.5
DVT/PE	57 (21.0)	32 (20.5)	25 (21.6)	0.9
PE	67 (24.6)	42 (26.9)	25 (21.6)	0.3
Nature of index event (270/272 patients)				
Unprovoked	217 (80.3)	126 (80.8)	91 (80.2)	0.2
Secondary to transient risk factor	53 (19.7)	30 (19.2)	23 (19.8)	1.0
Recurrent VTE	28 (10.4)	14 (9.0)	14 (12.1)	0.4

As shown in Table 4, during follow-up 15 major and CRNM bleeding events were recorded in the whole study population (rate 3.5 × 100 pt-yrs); 5 events were major bleeding (rate 1.2 × 100 pt-yrs), one of them (gastrointestinal in a patient on warfarin) was fatal; 6/15 bleeding events occurred among patients aged ≥90 years, all on DOACs treatment. One major bleeding was recorded in patients concomitantly treated with aspirin (rate 4.3 × 100 pt-yrs). Bleeding rates were higher in patients on DOACs than in patients on VKAs (HR 4.0; 95%CI 1.3–13.6; p = 0.01). These results are confirmed also when the analysis was limited to the first year of follow-up (Table 4). The difference was confirmed at the multivariate model; 4 of 9 bleeding events in patients treated with DOACs occurred on full dose treatment.

Overall, 8 thrombotic events were recorded during treatment (rate 1.9 × 100 pt-yrs); 2 were fatal (one each in patients on DOACs and on warfarin) (Table 4). The rate of thrombotic events was significantly higher in patients on DOACs than in patients on VKAs (HR 4.5; 95% CI 1.5–13.3); this difference was confirmed at the multivariate model and when the analysis was limited to the first year. Only 3 of these events were recurrences of VTE and no difference was detected between the 2 groups.

Mortality rates were lower in patients on DOACs than in those on warfarin, with a HR of 0.30 (95% CI 0.1;0.9), confirmed at the multivariate model (Table 4). These results are confirmed also when the analysis was limited to the first year of follow-up (HR 0.19, 95% CI 0.1–0.6).

4. Discussion

In this observational, prospective cohort study of very old patients on anticoagulant treatment for VTE, the bleeding risk was low despite the mean age of the population, with nearly 25% of patients older than 90 years at enrollment. The median duration of treatment was 19 months, thus showing that elderly patients enrolled in this study are maintained on anticoagulant treatment for a long period of time despite clinical guidelines suggesting stopping anticoagulation after 3 months in patients at high risk of bleeding, such as very old patients.

When we looked at the type of anticoagulant drug used, we found that patients on DOACs had higher rates of bleeding and also of thrombotic complications with respect to patients on warfarin; however, their mortality rate was markedly reduced.

The two groups had different baseline characteristics, a finding that is explained by the observational nature of the study. However, these differences did not reach statistical significance in the majority of cases, likely due to the relatively low number of enrolled patients. Patients on DOACs were significantly older and with a more prevalent history of previous bleeding or stroke/TIA events than patients on warfarin. On

Table 4
Adverse events during treatment.

	VKA (N = 156)	DOACs (N = 116)	Univariate	Multivariate[a]
	N (x 100 pt-yrs)	N (x 100 pt-yrs)	HR (95%CI)	HR (95%CI)
Bleeding events	6 (1.9)	9 (7.7)	4.7(1.5;15.0)	7.5(2.4;23.6)
Bleeding events at 12 months	1	3	5.1 (0.6;42.1)	6.2 (0.5;71.7)
Major bleedings	2 (0.6)	3 (2.6)		
Cerebral	1	0		
Gastrointestinal	1[c]	3		
CRNM bleedings	4 (1.3)	6 (5.1)[d]		
Soft tissue ematoma	1	2		
Gastrointestinal	2	1		
Other	1	3		
Thrombotic events	4 (1.3)	4 (3.4)	4.5 (1.5;13.3)	5.7 (1.6;20.3)
Thrombotic events at 12 months	0	4	–	–
Recurrent VTE	1 (0.3)	2 (1.7)		
Arterial events	3 (1.0)	2 (1.7)[b]		
Death for all causes	50 (16.0)	5 (4.3)	0.3 (0.1;0.9)	0.30(0.1;0.8)
Death at 12 months	15	3	0.33 (0.10;1.13)	0.19 (0.06;0.55)

[a] Adjusted for: age at enrollment, Sex, Diabetes mellitus, Hypertension, Frailty; COPD, Previous bleeding, Previous stroke, Active cancer, Renal Failure.
[b] Both patients treated with low-dose DOACs.
[c] fatal.
[d] 5 patients on low-dose regimen.

the contrary, as expected, severe renal failure was significantly more represented among patients on warfarin. The higher rate of bleeding observed in our DOACs cohort could be at least in part due to the higher prevalence of previous bleeding events in this group of patients. Similarly, the higher rate of previous cerebral ischemic events in this group of patients could explain the higher rate of stroke/TIA. Coleman et al. [11] reported data of a retrospective claim database analysis of patients with VTE with a median age of about 82 years, were the incidence of major bleeding was similar to that found in our cohort. However, in this study no difference was recorded between DOACs and VKAs. The low number of events recorded in our study could explain this discrepancy, but it should be noted that the median age of our patients was markedly higher, reaching about 88 years. Therefore, we cannot exclude that the very high median age of our patients may play a role in this observed difference.

It should be noted that only 5.5% of patients enrolled in our study were also on treatment with aspirin; yet the major bleeding rate in this group was three-fold higher than in patients without aspirin treatment.

Notwithstanding the generally low number of events recorded in the present study, a low rate of recurrent VTE was recorded during treatment in the two groups of patients, even if higher in patients on DOACs than in those on warfarin.

The use of low-dose regimen has not been tested in the registrative trials for the use of DOACs in acute VTE patients, with the exception of Hokusai study [12]. We found that about 45% of cases in our population were receiving a low-dose regimen even in the acute phase of the disease. This wide use of low dose regimen did not seem to affect the efficacy of treatment, considering that only two VTE recurrences were recorded among DOACs group, both in patients on full dose regimen. On the contrary, both the reported stroke/TIA events occurred in low-dose DOACs treated patients. In relation to the dose regimens of DOACs, we found that five out of nine bleeding events occurred in patients treated with low doses, suggesting that these patients were not protected from bleeding risk.

In our cohort, a much lower mortality rate was found among DOACs treated patients. In RCTs studies comparing DOACs versus warfarin treatment, no difference in mortality rate was found [13], but it should be noted that these trials have been conducted among patients with a median age highly younger than our patients. We may suggest that the higher mortality rate observed in patients on VKAs could be related, at least in part, to the selection criteria adopted by physicians in deciding the choice between the two anticoagulant regimens. In fact, the more complex clinical conditions of VKAs patients and the prevalence of severe renal failure may be one factor to explain the higher mortality rate recorded in these patients.

This study has a number of limitations. Firstly, the observational design requires extreme caution in interpreting direct comparisons between drugs due the intrinsic limitations and high risks of bias of these studies. Secondly, frailty was defined by using clinical items for dementia, bed rest and frequent falls that could be easily reported by the investigators, without the use of a validated, structured frailty stratification score. This explains the relatively low rate of the indicated items recorded in our cohort, where only very severe frailties were recorded. Third, the causes of death reported in the electronic files aimed to identify deaths related to bleeding events or cerebral ischemic events. All other causes of death have been defined as not related to anticoagulant treatment, including cancer, infectious diseases, vascular events (not cerebral), heart failure, renal failure, respiratory insufficiency, or sudden death. Finally, there was no central adjudication of outcome events in this study.

5. Conclusion

In conclusion, notwithstanding the long period of treatment widely adopted in Italian clinical practice - as it was in our cohort, we found that the rate of bleeding and thrombotic complications among very elderly VTE patients treated with oral anticoagulants was rather low. Patients treated with DOACs, despite a wide use of low-dose treatment, seemed to have a higher risk for bleeding than patients on warfarin. However, the DOACs low-dose regimens seemed to protect adequately the very elderly patients against VTE recurrence. Mortality was markedly lower in patients receiving DOACs.

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Declaration of competing interest

None declared.

Appendix A. List of the START2 register investigators

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References

[1] S. Barco, Y.W. Cheung, J.W. Eikelboom, M. Coppens, New oral anticoagulants in elderly patients, Best Pract Res Clin Haematol. 26 (2013) 215–224.

[2] P. Sardar, S. Chatterjee, S. Chaudhari, G.Y. Lip, New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials, J Am Geriatr Soc. 62 (2014) 857–864.

[3] G. Palareti, D. Poli, The prevention of venous thromboembolism recurrence in the elderly: a still open issue, Expert Rev Hematol. 11 (2018) 903–909.

[4] E. Antonucci, D. Poli, A. Tosetto, V. Pengo, A. Tripodi, N. Magrini, F. Marongiu, G. Palareti, The Italian START-Register on anticoagulation with focus on atrial fibrillation, PLoS One. 10 (2015) e0124719.

[5] C. Kearon, W. Ageno, S.C. Cannegieter, B. Cosmi, G.J. Geersing, P.A. Kyrle, Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH, J Thromb Haemost. 14 (2016) 1480–1483.

[6] F.R. Rosendaal, S.C. Cannegieter, F.J.M. Vandermeer, E. Briet, A method to determine the optimal intensity of oral anticoagulant therapy, Thromb Haemost. 69 (1993) 236–237.

[7] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, Nephron. 16 (1976) 31–41.

[8] R. Pisters, D.A. Lane, R. Nieuwlaat, C.B. de Vos, H.J. Crijns, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, Chest. 138 (2010) 1093–1100.

[9] S. Schulman, C. Kearon, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J Thromb Haemost. 3 (2005) 692–694.

[10] S. Kaatz, D. Ahmad, A.C. Spyropoulos, S. Schulman, Subcommittee on control of A, Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J Thromb Haemost. 13 (2015) 2119–2126.

[11] C.I. Coleman, A.G.G. Turpie, T.J. Bunz, J. Beyer-Westendorf, Effectiveness and safety of rivaroxaban versus warfarin in frail patients with venous thromboembolism, Am J Med. 131 (2018) 933–938 (e1).

[12] H.R. Buller, H. Decousus, M.A. Grosso, M. Mercuri, S. Middeldorp, M.H. Prins, G.E. Raskob, S.M. Schellong, L. Schwocho, A. Segers, M. Shi, P. Verhamme, P. Wells, Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism, N Engl J Med. 369 (2013) 1406–1415.

[13] N. van Es, M. Coppens, S. Schulman, S. Middeldorp, H.R. Buller, Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials, Blood. 124 (2014) 1968–1975.