DOACs dose adherence during initial and long term VTE management. Practical implications, findings from the RIETE registry.

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**Venous Thrombosis**
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**Objective:** Direct oral anticoagulants (DOACs) are available as alternatives to vitamin K anticoagulants (VKAs) for VTE management. Recently updated ACCP guidelines (February 2016) suggest using DOACs over VKAs for VTE treatment in non-cancer patients. Warfarin’s long half-life is an advantage for patients who occasionally miss doses compared with DOACs. Twice-daily dosing schedules may be more difficult for patients to adhere on the other hand the impact of a missed dose may be greater with DOACS. Medication adherence is important to attain good clinical outcomes with DOACs, especially in long term management asymptomatic patients. RIETE is a multicenter International Registry of VTE (more than 65000 patients enrolled from 245 centers) providing real life data on VTE presentation and management.

**Methods:** From 17194 patients enrolled in RIETE registry between 2013-16, 1445(8.4\%) received rivaroxaban and 81(0.47\%) apixaban as initial VTE treatment. Among 16123 patients, 2.403(15\%) received rivaroxaban and 315(2\%) apixaban as long term therapy. Patients receiving DOACs were usually younger than 50 years, without cancer and renal impairment and with normal body weight (Tables 1&2).

**Results:** 81.7\% of the patients received the recommended daily dose and 78\% the recommended twice daily schedule. When receiving DOACs active cancer patients and patients with renal insufficiency tend to receive lower doses. As far as long term treatment for VTE 87\% received the recommended daily dose, 6\% lower, and 6.8\% higher. Regarding daily regimen 90.4\% of patients received appropriate schedule. Patients that did not receive recommended doses were usually older, presented cancer and renal insufficiency. Patients that received DOACs in lower than recommended doses did not less bleeding. Interestingly patients that received DOACs in non recommended schedule or dose presented statistically more VTE recurrences Table 3 (HR 10.7, p<0.05)

**Conclusion:** When starting DOACs, physicians need to be aware of the various dosing and monitoring requirements for each agent, while patients need to be counselled regarding appropriate use of their medication. Inappropriate prescribing, monitoring and administration of DOACs occur frequently and expose patients to greater risk for VTE recurrence.
Patterns of VTE treatment with rivaroxaban in cancer patients – Results of the prospective Dresden NOAC registry (NCT01588119)

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Objective: For patients with cancer associated thrombosis (CAT), treatment with low-molecular weight heparin (LMWH) is recommended but direct oral anticoagulants such as rivaroxaban are used in some patients. However, data on characteristics and outcomes of CAT patients receiving rivaroxaban treatment in daily care are scarce. To evaluate the effectiveness and safety of CAT treatment with rivaroxaban in daily care

Methods: From the multicentric Dresden NOAC Registry a subgroup of cancer patients receiving CAT therapy with rivaroxaban was evaluated. Start of the prospective follow up (FU; phone visits at day 30 day and quarterly thereafter) was the start of rivaroxaban therapy.

Results: Of the 871 VTE patients receiving rivaroxaban for VTE in the registry, 121 patients (13.9%) also had a cancer diagnosis (mean age 70.3 years; 52.1% male; cancer reported as inactive in 74 cases, active in 34 cases and in 13 cases diagnosed after VTE diagnosis, 110 solid malignancies, 11 hematologic malignancies; table 1; figure 1).

During follow-up (mean 28.9 months, range 0.6 – 54.2), 11 patients (9.1 %) experienced recurrent VTE events (2 during rivaroxaban treatment, 9 after discontinuation or prolonged interruption >3d). Major bleeding occurred in 10 patients (8.3%) and predominantly occurred in patients with active cancer at baseline or diagnosed during VTE treatment (6/10).

24 patients died during FU (19.8%), of which 11 deaths occurred during or within 3 days after last intake of rivaroxaban. Most common causes of death were terminal malignant disease (n=11), followed by fatal cardiovascular event (n=4), age related death (n=4), fatal bleeding (n=3), sepsis/infection (n=1) and other reasons (n=1).

Conclusion: The majority of patients with cancer and VTE receive rivaroxaban only late after VTE diagnosis. For CAT patients with active cancer, LMWH is the predominant anticoagulant during the acute phase but a relevant number seems to be switched to rivaroxaban within weeks after VTE diagnosis. During rivaroxaban therapy, rates of recurrent VTE and major bleeding seem comparable to the rates seen with LMWH in CAT trials. Prospective RCTs should investigate the effectiveness and safety of rivaroxaban in CAT.
Survival and recurrent venous thromboembolism in 834 subjects after a first episode of isolated distal or proximal deep vein thrombosis without pulmonary embolism

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Objective: Isolated distal deep vein thrombosis (iDDVT) may be associated with a reduced risk of recurrent venous thromboembolism (VTE) if compared to proximal DVT (pDVT) or pulmonary embolism (PE). However, a few studies focused on patients without previous VTE events. Furthermore, the risk of death following iDDVT has never been investigated.

Our cohort study included consecutive individuals followed at a single institution (years 2004-2012) diagnosed with a first-episode index iDDVT or pDVT without (a)symptomatic PE. Death and VTE recurrence rates were compared between the two groups.

Methods: Primary outcomes: i) all-cause death, ii) symptomatic recurrent PE or pDVT. Three independent investigators retrieved clinical data from patients’ charts and three adjudicated the outcomes. All patients were routinely scheduled for a yearly clinical control and contacted telephonically if they missed a follow-up visit.

Results: A total of 4,759 medical records were screened and 834 subjects included for the purpose of this study. Of those, 203 had symptomatic iDDVT and 631 had pDVT associated (n=227) or not (n=404) with distal DVT.

One-hundred twenty-six recurrent symptomatic pDVT or PE were recorded during follow-up, of which 110 after index pDVT (17.4%) and 16 after iDDVT (7.9%) for rates of 4.5 events/100 patient-years (95CI 3.7-5.4) and 2.0 events/100 patient-years (95CI 1.1-3.2), respectively. Patients with recurrent symptomatic PE during follow-up were 2.5% (of pDVT patients) and 3.0% (of iDDVT patients). After adjustment for length of anticoagulant treatment, age, sex, and DVT risk factors, index iDDVT was associated with a reduced risk of symptomatic recurrent pDVT or PE (adjusted Hazard Ratio 0.32 [95CI 0.19-0.55]).

Death occurred in 264 patients (31.7% [95CI 28.6%-34.9%]) during 5,491 patient-years of follow-up: 52 had had iDDVT (25.4%) and 212 pDVT (33.6%). One-year mortality was 12.2% in the two groups. The long-term hazard of death appeared reduced in iDDVT patients (adjusted Hazard Ratio 0.58 [95CI 0.26-1.30]), if only unprovoked events were considered.

Conclusion: iDDVT patients were at a reduced risk of recurrent VTE and long-term death compared to pDVT. One-year mortality was mostly due to active cancer and appeared similar between iDDVT and pDVT groups.
Clinical outcomes of a management strategy consisting of tailored anticoagulant treatment based on residual vein thrombosis: contemporary data

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**Venous Thrombosis**

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**Objective:** Finding the optimal duration of anticoagulant treatment following an acute event of deep venous thrombosis (DVT) is challenging. Residual thrombosis has been identified as risk factor for recurrence, but data on management strategies based on residual thrombosis and associated recurrence rates in defined clinical care pathways (CCP) are lacking.

**Methods:** All patients treated at Maastricht University Medical Center within an established clinical care pathway from June 2003 through June 2013 were prospectively followed for up to 11 years. Treatment duration was tailored based on residual vein thrombosis. Recurrence rates were determined. A cox proportional hazards model employing anticoagulation treatment as time-varying covariate was used to define risk factors for recurrence.

**Results:** Out of 479 patients diagnosed with proximal DVT, 474 completed the two-year CCP (99%), and 457 (94.7%) the extended follow-up (2231.2 patient-years; median follow-up 4.6 years; median age 58.0 years; 50.4% females). Overall VTE recurrence was 2.9 per 100 patient-years, 1.3 if provoked by surgery, 2.1 if a non-surgical transient risk factor was present, and 4.0 if unprovoked. Residual thrombosis was present in 141 patients (29.8%). Duration of anticoagulation was 3 months in 75 patients (15.8%), 6 months in 230 (48.1%), 12 months in 95 (20.1%) and indefinite in 76 (16%). Significant predictors of recurrent events were unprovoked VTE (hazard ratio [HR] 4.6; 95% CI 1.7, 11.9), elevated d-dimers one month after stop treatment (HR 3.3; 1.8, 6.1), male sex (HR 2.8; 1.5, 5.1), high factor VIII (HR 2.0; 1.1, 3.7) and use of contraceptives (HR 0.1; 0.0, 0.9).

**Conclusion:** Patients with DVT managed within an established clinical care pathway according to the presence of residual vein thrombosis had low incidences of VTE recurrence. In accordance with other clinical settings, unprovoked VTE, male sex, elevated D-dimers one month after stop treatment, inflammation, and high FVIII were identified as major predictors for recurrent VTE.
Innate effector-memory T cell activation regulates post-thrombotic vein wall inflammation and thrombus resolution

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Objective: This study investigated the functional role of T cells in venous thrombosis.

Methods: Deep vein thrombosis (DVT) was induced by 80% flow reduction in the inferior vena cava (IVC) of mice. T cell recruitment and inflammatory activity was followed by flow cytometry, histology and intrathrombotic gene expression in reporter strains and upon depletion of T cells over various time points after DVT.

Results: DVT recruits effector-memory T cells into the vein wall and thrombus. Recruited effector-memory T cells experience an immediate antigen-independent activation and produce IFN-gamma in situ. Effector-memory T cell-derived IFN-gamma determines neutrophil and monocyte recruitment and delays thrombus neovascularization and resolution.

Conclusion: Effector-memory T cells orchestrate the inflammatory response in venous thrombosis affecting thrombus resolution.
Genotype phenotype association in a large cohort of subjects with protein C or protein S deficiency

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Objective: Hereditary deficiencies of natural anticoagulant proteins including protein C (PC) and protein S (PS) are known causes of inherited thrombophilia. We aimed to assess the performance of genetic analysis of PROC and PROS1 with relation to PC and PS assay data.

Methods: In a retrospective cohort study we genotyped 314 subjects with PC and 460 subjects with PS deficiency. Mutations were detected by direct sequencing of the coding regions including splice sites of PROC and PROS1. We performed multiplex ligation dependent probe amplification in order to reveal large copy number variations. PC and PS assay data were provided by external centres. Statistic methods of logistic regression and receiver operating characteristic curve analysis were applied to evaluate the correlation between laboratory status and inherited deficiencies and to propose cut-off values for the indication of genetic testing.

Results: Mutations were identified in 226 patients of the PC and 197 patients of the PS deficiency cohort, correlating with an overall mutation detection rate (MDR) for PROC of 72% and PROS1 of 43%, respectively. Both cohorts had a similar mutation profile with the highest prevalence for missense mutations (81% in PC, 60% in PS). MDR correlated negatively with PC and PS levels. In addition, we observed a clear correlation between laboratory data and the type of mutation. For PC activity we determined a cut-off value of 61% with a sensitivity of 81% and a specificity of 64% for revealing a causal gene mutation. Within the PS cohort factor V Leiden (FVL) showed a significant influence on MDR. For individuals without FVL the proposed cut-off value for PS activity is 45% associated with a sensitivity of 70% and a specificity of 65%. In states of acquired reduction due to vitamin K antagonist intake or pregnancy lower cut-off values for PC (44%) and PS (21%) were calculated.

Conclusion: Our findings suggest that in patients with PC activity below 61% and PS levels (activity or free antigen) below 45% genetic analysis represents a useful diagnostic tool to confirm inherited PC and PS deficiency. In addition, in the presence of FVL and acquired deficiency states adjusted cut-off values might be applied.