Editorial

Thromboprophylaxis after hospital discharge in acutely ill medical patients: need for trials in patients who are at high risk of venous thrombosis

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Venous thrombosis (VT), composing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a commonly occurring complication following hospitalization. Patients hospitalized for acute medical illnesses, such as heart failure, respiratory failure, a flare of inflammatory bowel disease or acute neurologic disease have an eightfold risk for the development of VT as opposed to the general population (1). For this reason, guidelines advise to prescribe in-hospital thromboprophylaxis to reduce the rate of symptomatic VT in acutely ill medical patients (2). Randomized, controlled trials of anticoagulants *vs.* placebo in such hospitalized medical patients have shown a reduction of more than 50% in the rate of VT, that outweighed the small absolute increase in major bleeding (3). For this reason guidelines recommend the use of low-dose anticoagulants among patients at high risk for thromboembolism for 6 to 14 days but advise against extended-duration thromboprophylaxis after hospital discharge (2,4). However, the duration of this thromboprophylaxis is disputed because of several reasons. First, physicians have to weigh the benefits of prolonged treatment against the risks such as major and clinical relevant non-major bleeds introduced by anticoagulant therapy (5). Second, literature shows that, the risk of VT remains markedly increased for at least the first month after hospital discharge (6). And third, the heterogeneity of hospitalized medical patients makes it difficult to translate results derived from earlier trials (that studied the efficacy of extended thromboprophylaxis therapy) to individual patients (7). For instance, extended duration low-molecular weight heparin has seemed to prevent VT more than it increased major bleeding events only in patients with immobility, the elderly or women (5).

In an attempt to answer this dispute, A.T. Cohen and colleagues studied whether extended thromboprophylaxis with betrixaban in acutely ill medical patients is an effective and safe method for the prevention of VT (APEX trial), results were recently published in the N Eng J Med 2016;375:534-44 (8). The authors performed a randomized, double-blind, double-dummy, active-controlled, multinational clinical trial in which acutely ill medical patients were randomized to receive either subcutaneous enoxaparin (10±4 days) plus oral betrixaban placebo once daily (35 to 42 days) or subcutaneous enoxaparin placebo (10±4 days) and oral betrixaban once daily (35 to 42 days). Analyses were stratified by three cohorts: patients with an elevated D-dimer level at baseline (cohort 1), patients with an elevated D-dimer level or an age of at least 75 years (cohort 2) and the overall study population cohort (cohort 3). Mean age of all participants was 76 years and nearly half of the population was men (45%). Patients were hospitalized for heart failure (45%), infection (29%), respiratory failure (12%), ischemic stroke (11%) or rheumatic disorders (3%).

The primary efficacy outcome (a composite of asymptomatic proximal DVT and symptomatic VT) occurred in 6.9% in the betrixaban group and in 8.5% in the enoxaparin group (cohort 1) for a relative risk (RR) of 0.81 [95% confidence interval (CI), 0.65 to 1.00]. Comparable RRs were found for cohort 2 (RR =0.80; 95% CI, 0.66 to 0.98) and cohort 3 (RR =0.76; 95% CI, 0.63 to 0.92). A composite endpoint of major and clinical relevant non-major bleeding was diagnosed in 3.1% in the betrixaban group as compared with 1.9% in the enoxaparin group for a RR of 1.64 (95% CI, 1.13 to 2.37). Similar results were found within cohort 2 and 3 (RRs of 1.89 and 1.97, respectively). From the APEX trial it was concluded that among patients hospitalized for acute medical illnesses, there was no benefit for a treatment regimen of extended duration with betrixaban *vs.* standard duration of enoxaparin.

This finding corroborates on previous trials such as the ADOPT and MAGELLAN trial, which failed to establish efficacy of extended thromboprophylaxis for the prevention of symptomatic DVT and PE in acutely ill medical patients (9,10). Conversely, these previous trials showed that an extended regimen with anticoagulants resulted in more major bleedings (ADOPT trial, RR for major bleeding 2.53, 95% CI, 0.98 to 6.50 and MAGELLAN trial RR =2.87; 95% CI, 1.60 to 5.16), a finding which could not be replicated in the APEX trial, though more clinical relevant bleedings occurred in the extended therapy group.

Overall, these trials do not support extended thromboprophylaxis in acutely ill medical patients. If we assume an absolute risk reduction of 0.6% for the prevention of symptomatic VT and an absolute risk increase of about 1.2% for major and clinical relevant non-major bleeds (according to the results from a major secondary efficacy outcome in cohort 1 in the APEX trial), the number needed to harm (NNH) [83] would outweigh the number needed to treat (NNT) [167]. Therefore there is, in our opinion, no indication from the APEX trial to extend thromboprophylaxis to all medical patients. However, results from extended thromboprophylaxis trials in medical patients leave room for high-risk patients that could still benefit from extended treatment (8,10) because their absolute thrombosis risk is higher. Thus, the NNT will decrease as a result of an increasing absolute risk reduction. Many studies tried to predict a high VT risk in acutely ill medical patients and the IMPROVE-7 and PADUA score are currently the best performing models that have been developed (11,12). Results from the APEX trial suggest that in future thromboprophylaxis trials high-risk hospitalized medical patients are randomized at discharge to receive thromboprophylaxis or placebo for a prolonged duration. This approach has been adopted in the MARINER trial, which uses a validated risk assessment model (IMPROVE VTE) and D-dimer determination to identify patients at high risk of VT, of which results need to be awaited (13).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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