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Old and new risk factors for upper extremity deep venous thrombosis - reply to a rebuttal

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extremity DVT [5]. The type of the central venous catheter influences the rate of thrombotic complication [6]. Infections of central venous catheters increase the risk of catheter-related thrombosis in patients with malignancy [7]. Prophylaxis of venous thromboembolism with heparin, low-molecular-weight heparin or low-dose warfarin may reduce the incidence of catheter-related thrombosis, which is however, not yet a standard procedure, as discussed by the authors [8].

These risk factors and the prophylactic measures have not been documented in the study and may substantially influence the reported data. Thus, the data does not support the conclusion that central venous line alone is, a very strong risk factor for arm vein thrombosis. The present data only indicate an increased risk for upper extremity DVT by the combination of central venous line and chemotherapy. Additional information on the type of central venous catheter, concomitant infection, the type of the central venous line and the use of anticoagulants in or out of hospital would define precisely the risk factors for upper extremity DVT and the outcome of the patients.

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In their comment, Harenberg and Mannheim [1] postulate that our large population-based case–control study on risk factors for upper extremity deep venous thrombosis (UE-DVT) [2] only indicates an increased risk for the combination of a central

venous catheter (CVC) and chemotherapy and that information on additional parameters, such as type of CVC, concomitant infection, or anticoagulant prophylaxis, is needed to define precisely the risk factors for UE-DVT for patients with a CVC. Indeed, the risk of UE-DVT in a patient with a CVC is the result of the interaction between numerous patient-related factors, acquired as well as genetic risk factors, including CVC-related factors. In this *Journal*, a review of risk factors for CVC-related thrombosis is given by van Rooden *et al.* [3].

In our study, patients with a CVC (mostly cancer patients who received intensive chemotherapy) had a highly increased risk of UE-DVT (OR_{adj} 1136, 95% CI: 153–8448) compared with patients who had not used a CVC, in whom UE-DVT is

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rare. For patients with a CVC without cancer, the odds ratio was, however, also high, indicating a more than 250-fold increased risk compared with those without a CVC (OR_{adj} 262 95% CI: 30–2288), which shows the thrombogenicity of these devices. Certainly, chemotherapy could induce a systemic hypercoagulable state, which may increase the risk of CVC-related thrombosis. However, chemotherapeutic agents and other medication are delivered into the bloodstream at the level of the superior caval vein/right atrium, whereas CVC-related thrombosis in the majority of cases is located at a more proximal level than the superior caval vein/right atrium [3]. Another argument in favor of the CVC itself as the major trigger comes from a large observational study in patients with CVC-related thrombosis receiving intensive chemotherapy, where the contra-lateral vein segments, regularly inspected by ultrasound, were usually free of thrombosis [4]. Analogously to our findings, it has been demonstrated that patients with pacemaker leads, who are free of cancer and prothrombotic medication, also have an increased risk of thrombosis [5]. Pathophysiologically, a plausible explanation is that the presence of a CVC, as a non-biological surface in the bloodstream, activates the coagulation pathway, or induces endothelial trauma caused by the indwelling CVC or insertion procedures, or both [3]. Other risk factors may additionally contribute to the occurrence of thrombosis, such as concomitant infection or a prothrombotic state because of thrombophilia, malignancies, or certain drugs.

The need for anticoagulant prophylaxis for CVC-related thrombosis is still debatable. Despite initial recommendations in 2001 [6], anticoagulant prophylaxis was given to only 10–20% of the Dutch Oncology and Haematology Departments in patients who received a CVC for intensive chemotherapy [7]. The latest guidelines of the ACCP (2004) do not recommend anticoagulant prophylaxis [8]. Recently, in several large trials, no beneficial effect was obtained from anticoagulant prophylaxis [9–11] in patients with a CVC. We therefore do not believe that these changes in the policy on anticoagulant prophylaxis have influenced our estimates.

Central venous catheter-related characteristics, such as type of catheter, concomitant infections, and therapy administered through the catheter or anticoagulant prophylaxis, were not recorded in our study, as this was not the primary goal. In our study, patients with UE-DVT were analyzed for various risk factors of DVT. Patients had been treated in a large number of

hospitals in the western part of the Netherlands, which therefore most likely represents various CVC-related policies. In conclusion, we believe that our study gives a representative overall risk-estimation for the group of patients with a UE-DVT in general, including the substantial effect caused by CVC.

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