Is there a true difference in recurrence rate of deep venous thrombosis between men and women?

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The 2-year cumulative recurrence rate of deep venous thrombosis after suffering a single episode of thrombosis is approximately 10%–18% [1,2]. Recently, it was shown that the risk of recurrent venous thrombosis is higher among men than women, a difference that appeared not to be due to discontinuation of oral contraceptives or hormone replacement therapy, the presence of the factor V Leiden (FV Leiden) or the prothrombin mutation, or elevated levels of factor VIII or IX (FVIII or FIX) [3,4].

The diagnosis of recurrent deep venous thrombosis in the previously unaffected leg, i.e. the contralateral leg, is not associated with diagnostic problems that may occur due to residual thrombus mass or damage to the vessel wall caused by previous thrombosis. However, the diagnosis of recurrent deep venous thrombosis in the same leg as the first event, i.e. the ipsilateral leg, is much more difficult. Therefore, we considered that the difference in recurrence rate between men and women might be explained by a higher number of men presenting with false positive, ipsilateral recurrences, indicating that the excess recurrences in men are residual thrombi or post-thrombotic syndrome rather than new deep venous thromboses.

Analyses were performed in a large prospective follow-up study, the Cambridge Venous Thromboembolism (CVTE) study. The design of this study was described in detail previously [2]. In brief, 570 patients with a first, objectively diagnosed episode of deep venous thrombosis of the leg or a pulmonary embolism, who registered at Addenbrookes NHS Trust hospital in Cambridge between August 1997 and January 2002, were followed-up for 2 years after discontinuation of anticoagulation therapy. Patients with malignant disease at the time of registration, antiphospholipid syndrome, cerebral vein thrombosis, continued anticoagulant therapy, or proven recurrent deep venous thrombosis during anticoagulant therapy were excluded. For the current study, we only included patients with a first episode of deep venous thrombosis of the leg. Only patients with a new or extended clot, resulting in restarting anticoagulation therapy, were recorded as recurrent deep venous thrombotic events.

Recurrence rates were compared between men and women using Kaplan-Meier estimates and Cox proportional hazards modeling.

In total, 385 patients with a first episode of deep venous thrombosis of the leg were included in this study, 177 men and 208 women. Table 1 shows the number of recurrences that occurred during the follow-up. During follow-up, in total 30 patients had a recurrent deep venous thrombosis of the leg (7.8%). Twenty-two out of 177 men and eight out of 208 women had a recurrent event during follow-up, indicating that the total cumulative proportion of recurrent deep venous thrombosis after two years of follow-up was higher among men compared with women, i.e. 12.4% and 3.8%, respectively (HR = 3.4; 95% CI: 1.5–7.6). This difference only marginally changed after exclusion of surgery and pregnancy related thrombotic events (HR = 3.3; 95% CI: 1.4–7.3).

Twenty-two patients (16 men and six women) were diagnosed with a recurrent deep venous thrombosis in the same leg as their first thrombotic event (ipsilateral), whereas eight patients (six
men and two women) were diagnosed with a recurrent deep venous thrombosis in the opposite leg (contralateral).

Since the diagnosis of recurrent deep venous thrombosis in the ipsilateral leg is associated with more diagnostic problems, we calculated the risk of a recurrent deep venous thrombosis in men compared with women, considering only the contralateral recurrences as true recurrent events. The risk of a (contralateral) recurrence is 3.8-fold higher in men compared with women (HR = 3.8; 95% CI: 0.8–19.0). Again, exclusion of surgery or pregnancy related venous thromboses did not alter the results (HR = 3.7; 95% CI: 0.7–18.4).

Two previous follow-up studies showed that men have a much higher risk of recurrent deep venous thrombosis compared with women; a difference that currently remains unexplained [3,4]. We hypothesized that there might not be a true difference between men and women but that this supposed difference is due to a higher number of false positive, ipsilateral recurrences in men compared with women, indicating that the excess recurrences in men are residual thrombi or post-thrombotic syndrome rather than new deep venous thromboses. However, the results of this study indicate there appears to be a true difference in recurrence rate between men and women, which cannot be explained by a higher incidence of false positive ipsilateral recurrences in men.

Future studies should focus on the reason why men are at increased risk of recurrent thrombosis as compared with women. Although a number of precipitating factors have been studied already, e.g. oral contraceptive and hormonal replacement therapy, the FV Leiden or the prothrombin 20210A mutation, and high levels of FVIII or FIX, these do not explain the difference in recurrence risk. Possibly, yet unknown risk factors will explain this risk difference in the future. Global hypercoagulability tests such as the endogenous thrombin potential might be useful in demonstrating a truly increased thrombotic potential in men compared with women after suffering a first thrombotic event.

References

**Table 1** Number of recurrent deep venous thrombotic events (cumulative proportion of recurrent deep venous thrombosis)

<table>
<thead>
<tr>
<th></th>
<th>Total study population n (%)</th>
<th>Men n (%)</th>
<th>Women n (%)</th>
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<tbody>
<tr>
<td>n total</td>
<td>385 (100)</td>
<td>177 (100)</td>
<td>208 (100)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30 (7.8)</td>
<td>22 (12.4)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>8 (2.1)</td>
<td>6 (3.4)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>22 (5.7)</td>
<td>16 (9.0)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>No recurrent DVT</td>
<td>355 (92.2)</td>
<td>155 (87.6)</td>
<td>200 (96.2)</td>
</tr>
</tbody>
</table>

*Percentages of total are calculated within each group.

**Activation of hemostasis is associated with early cognitive decline after off-pump coronary artery bypass surgery**

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Cognitive dysfunction after coronary artery bypass grafting (CABG) is a well-recognized complication and has been largely attributed to the use of the cardiopulmonary bypass (CPB) system [1,2]. However, several studies have demonstrated that off-pump CABG is also associated with cognitive decline, suggesting that other factors than the use of CPB can contribute to this complication [3,4]. Recently, we demonstrated that off-pump CABG is associated with postoperative activation of hemostasis to a similar extent as conventional CABG in the later postoperative period [5]. This postoperative