

# Does androgen-deprivation therapy for prostate cancer increase the risk for thromboembolic disease?

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**V**enous thromboembolism (VTE) is a common complication of cancer. Compared to other types of cancers, such as pancreatic and lung cancer, prostate cancer (PCa) is associated with relatively lower rates of this complication.<sup>1-3</sup> However, it is reasonable to believe that the risk for VTE may be higher in PCa patients who are treated with androgen-deprivation therapy (ADT) because it can alter both tumour and host factors that facilitate the development of VTE.

In this issue of the journal, Othman et al provide data from a comparative, prospective thromboelastographic analysis of PCa patients initiating ADT, and two control groups — PCa patients on watchful waiting and healthy men. Thromboelastography (TEG) is a laboratory method that assesses the strength and elasticity of a clot and, thus, depends on the global function of different hemostatic processes, including plasma coagulation factors, platelet function, and fibrinolysis. A previous study by the same group suggested that PCa patients, in particular patients with advanced disease who receive ADT, have hypercoagulability that can be identified by TEG.<sup>4</sup> Here, the authors confirmed these findings, but could not demonstrate a consistent effect of ADT on hypercoagulability as defined by TEG over time.

The interactions between PCa in general and ADT in particular with VTE development are complex and are obviously not only a reflection of global hypercoagulability laboratory parameters. Factors such as disease burden, advanced age, immobilization, fractures, and cardiovascular disease, which are associated with either the indications for ADT or its associated complications, increase the risk of VTE development in this patient population. Indeed, analyses of different administrative registries suggest an association between ADT use and thromboembolic events.<sup>5,6</sup> Using the Surveillance, Epidemiology and End Results (SEER)-Medicare

database, Ehdaie et al analyzed the rate of VTE in 154 611 PCa patients, of whom 58 466 (38%) received ADT, and show that ADT is associated with 56% increased risk of VTE, in particular in patients receiving long-term ADT.<sup>5</sup> Klil-Drori et al analyzed a cohort of 21 729 PCa patients from the U.K. Clinical Practice Research Datalink and found that current, but not past, ADT is associated with an overall 84% increased risk of VTE.<sup>6</sup> While subjected to known limitations of observational studies, these studies and others<sup>7,8</sup> suggest a link between ADT and the risk of VTE, in particular with longer treatment. Ongoing studies in PCa that prospectively collect cardiovascular and thromboembolic data will hopefully be able to re-examine these findings. In the interim, a question that comes to mind is whether there is any value for thromboprophylaxis in PCa patients with advanced disease in general and those on ADT in particular?

In general, routine thromboprophylaxis is not currently recommended in ambulatory cancer patients except for patients with myeloma.<sup>9</sup> ADT in PCa patients with specific risk factors (immobilization, paralysis due to spinal cord compression, or previous VTE), however, calls for consideration of thromboprophylaxis. The specific mode of ADT also needs to be factored into the individual risk for VTE, as different modes of ADT associate with different risks for VTE development. It has been well-demonstrated that oral estrogen is associated with hypercoagulability<sup>10</sup> and significant thromboembolic risk, which actually led to its abandonment as an optional primary mode of ADT in PCa.<sup>11</sup> There are indications from observational studies that there may be differences in the risk of VTE between other forms, combinations, or sequences of ADT.<sup>6,8</sup>

Taken together, while we are waiting for confirmatory data from prospective cohort studies, physicians treating advanced PCa patients should be aware that these patients may be at an increased risk of developing thromboembolic events, especially when exposed to long-term ADT.

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