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European Association of Urology

Platinum Opinion

# Recommendations to Balance Benefits and Risks Of Thromboprophylaxis and to Avoid Central Venous-access Devices During First-line Chemotherapy in Men with Metastatic Germ Cell Tumors: The European Association Of Urology Testicular Cancer Panel Position in 2021

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Recent randomized controlled trials have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and reported a relative risk reduction of 30–60% in venous thromboembolic events (VTEs) but a doubling of bleeding risk [1–4]. Based on these results, the most recent American Society of Clinical Oncology clinical practice guideline update recommends thromboprophylaxis with apixaban, rivaroxaban, or low-molecular–weight heparin (LMWH) for cancer patients with a high risk of VTE and low risk of bleeding [5]. Patients with metastatic germ-cell tumor (mGCT) were under-represented in all trials and thus it is not clear whether this recommendation applies to this group, although retrospective data suggests similar efficacy of VTE prophylaxis [6].

Several more recent retrospective cohort studies published mGCT-specific VTE and bleeding risks as well as potential VTE risk factors. In the largest multicenter cohort study, the cumulative VTE incidence for men with mGCT was 11%, of which <1% were fatal [7]. Nearly all VTEs occurred shortly before or during the first 90 d of chemotherapy [7]. Bleeding was observed in 0.5% (95% confidence interval [CI] 0.02–1%) of men not on thromboprophylaxis, 2.5% (95% CI 0.3–8.8%) of men on thromboprophylaxis, and 3.6% (95% CI 1.2–8.3%) of patients fully anticoagulated because of VTE [7]. Cumulative VTE incidence of 5% during or after chemotherapy occurred in men without any risk factors for VTE. This would translate to a number needed to treat of 32–55, depending on the efficacy assumed for thromboprophylaxis [8]. If thromboprophylaxis resulted in a similar reduction in VTE risk and increase in bleeding risk as those observed in other cancers [1–4], the relative risk of VTE might decrease by 30–60%.

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This would translate to an absolute risk reduction from 5–10% to 2–5% and an increase in the absolute risk of bleeding from <1% to approximately 2–3% [8].

Critics of thromboprophylaxis in mGCT argue that the interobserver reliability for detecting incidental asymptomatic VTEs on staging scans is poor and that some asymptomatic VTEs may only represent artifacts. Nevertheless, only <1% of mGCT cases have asymptomatic VTEs detected on staging scans [8]. Furthermore, incidental VTEs may not truly be asymptomatic, as affected patients may have mild symptoms such as cough and fatigue that may be misinterpreted because of the underlying cancer or its associated treatment.

Advocates of thromboprophylaxis contend that a reduction in VTE risk may improve outcomes as VTE can be directly fatal in <1% of cases or indirectly fatal. An immediate initial consequence of a VTE is the need for therapeutic anticoagulation, which is associated with a higher risk of clinically significant bleeding [8,9], including critical areas, particularly intracerebral bleeding, and can complicate postchemotherapy surgery. VTE may also result in long-term complications including post-thrombotic syndromes, which can lead to venous leg ulceration and chronic pain. Similarly, pulmonary embolism can impair right ventricular function and pulmonary arterial pressure that does not resolve in 10–30% of patients, with up to 4% ultimately developing chronic symptomatic pulmonary hypertension [10]. These complications all reduce quality of life and increase lifetime health care costs.

On the basis of disease-specific VTE risk assessments in numerous retrospective cohort studies and the long life expectancy of mGCT patients, the European Association of Urology Testis Cancer Guideline panel has discussed a recommendation regarding thromboprophylaxis. All members agreed that men with mGCT undergoing chemotherapy are at high risk of VTE and low risk of bleeding. Although several mGCT-specific VTE risk factors have been described in the literature (Supplementary Table 1), only data from retrospective cohorts are available, VTE outcome definitions are heterogeneous and in most of the studies only univariable analyses without external validation were performed. Given the apparent high VTE incidence and only nonvalidated VTE risk factors, the panel preferences were divided between members who favored thromboprophylaxis in all men and members who would restrict thromboprophylaxis to men with certain risk factors. For the final guideline recommendation, the panel agreed that on the basis of the current literature, only a generic statement about the use of thromboprophylaxis is warranted until stronger evidence is available (Table 1). Therefore, randomized controlled trials or well-conducted prospective cohort studies with an adequate sample size allowing adjustment for potential confounders and numerous risk factors are needed to clarify the indication for thromboprophylaxis. This generic statement in the testis cancer guideline should remind clinicians about the high VTE incidence and to prescribe thromboprophylaxis after balancing the risks and benefits. In addition, the majority of the panel agreed that a central venous-access device should be avoided whenever possible as this was the only modifiable risk factor that remained significantly associated with VTE in a multivariable risk prediction model [8].

**Table 1 – New recommendations to reduce the risk of venous thromboembolic events in men with metastatic germ-cell tumor undergoing chemotherapy in the testis cancer guideline of the European Association of Urology**

| Recommendation | Strength rating |
|---|---|
| Balance the individual patient's potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumors | Weak |
| Avoid use of a central venous-access device during first-line chemotherapy whenever possible | Weak |

Thromboprophylaxis includes either LMWH or oral thromboprophylaxis (apixaban 2.5 mg twice daily or rivaroxaban 10 mg daily) starting before chemotherapy and continued for at least 90 d. Thromboprophylaxis should only be prescribed if no drug interactions or significant risk factors for bleeding are present. Although GCT-specific risk factors for bleeding are ill defined, the personal experience of panel members and case reports suggest that men with organ infiltration, cerebral metastases, and/or significantly elevated β human chorionic gonadotropin levels suggestive of choriocarcinoma are at higher risk of bleeding (Supplementary Table 1).

***Conflicts of interest***: Karim Fizazi has participated in advisory boards for/received institutional honoraria from Amgen, Astellas, Bayer, Curevac, Janssen, MSD, Orion, and Sanofi. Joost L. Boormans has been a company consultant with receipt of honoraria or consultation fees for MSD, has participated in a company-sponsored speaker bureau for Ipsen Farmaceutica, has participated in a trial for Janssen Cilag, and has received grants/research support from GenomeDx Bioscience. Javier Mayor de Castro has participated in trials for Bayer and Astellas. The remaining authors have nothing to disclose.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.02.032.

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