

Comorbidity and the Risk of Venous Thromboembolism in Prostate Cancer

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Venous thromboembolism (VTE) includes the development of deep vein thrombosis (DVT) and pulmonary embolism (PE).^{1,2} VTE is common in the general population (risk, 118 per 100,000 person-years), and PE is associated with a 30% risk of death within 3 months.^{3,4} Important risk factors for VTE include increasing age, recent surgery, and malignancy.^{2,3} Additional VTE risk factors include trauma, institutionalization, and specific comorbidities, including myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, and certain neurologic disorders.^{3,5,6} Effective and safe thromboprophylaxis and treatment exist.^{6,7}

VTE is particularly important in the cancer population. Individuals with a diagnosis of cancer have a 4-fold increased risk of developing VTE.¹ The frequency of VTE is higher in the first year after a diagnosis of cancer.⁸ In addition, survival among individuals with cancer who have a VTE is 3 times worse than that among individuals who have cancer and no occurrence of VTE.^{1,9} Not only does a diagnosis of cancer increase the risk of VTE: site, stage, and treatment all appear to influence the risk.^{1,8} Among cancer sites, high-risk cancer types include brain, lung, and pancreatic and other digestive cancers.^{1,9} Prostate cancers (PCs), as well as breast and colorectal cancers, are considered to fall within the low-risk category compared with most other malignancies.^{1,9} As disease stage progresses, so too does the likelihood of VTE occurrence.⁸ Furthermore, treatment for the disease can also impact the risk of VTE occurrence; surgery and chemotherapy increase the risk of VTE, whereas radiation is not typically considered a risk factor.^{1,10}

The major risk factors for VTE in the general population and the overall cancer population hold true for men with PC. Age and active malignancy increase the risk of VTE, and recent surgery is associated with a 5-fold to 7-fold increased risk.¹¹ Like all cancer types, more advanced stage is associated with an increased risk of VTE.¹² Additional factors that can increase the risk of VTE in men with PC include a previous history of VTE, blood transfusion, ABO blood type, the number of lymph nodes removed during surgery, and receipt of androgen-deprivation therapy (ADT).^{11,13,14} ADT in particular deserves special comment, because it is received by up to 1 in 2 men with PC¹⁵ and may increase the risk of both arterial thromboembolism and VTE by up to 50%.¹³ Both treatment and duration of ADT increase an individual's risk of a VTE occurrence.¹³

There are still areas that need to be addressed to obtain a fuller understanding of the risk of VTE for men diagnosed with PC who are undergoing various treatments (surgery, radiation, or ADT). Although some risk factors have been identified consistently across multiple studies, including increasing age, recent surgery, and active malignancy, the role of other risk factors, such as blood type, vascular or neurologic disorders, other comorbidities, and receipt of ADT, needs to be evaluated further. What is not so clear is how these VTE risk factors interact with one another. Risk factors (eg, PC, comorbidity) for a given outcome (eg, VTE) can interact in 1 of 3 main ways: they may be additive, multiplicative, or partially offset one another. Although much of conventional medicine features additive risk factor models, there are important exceptions. For example, in the world of inheritable thrombophilias and VTE risk, being heterozygous for Factor V Leiden (FVL) is associated with a 4-fold increased risk of VTE, whereas being homozygous is associated with an 11-fold increased risk.¹⁶ Family members who are heterozygous for the FVL mutation have a 3.5-fold increased risk of VTE, but those who are homozygous have a whopping 18-fold increased risk.¹⁷ Understanding the relation between risk factors may have important implications for counseling, screening, and prophylaxis.

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In this issue of *Cancer*, a Danish group led by Ording has attempted to address the relation between PC and comorbidity on VTE risk.¹⁸ The authors used the Danish Cancer Registry to identify 44,035 patients with PC and matched them on age, year, and comorbidities to non-cancer controls from the general population at a 1:5 ratio. Patients with prior VTE were excluded. Cancer and non-cancer cohorts were followed for a median of 3.2 years and 4.5 years, respectively, for the occurrence of inpatient or outpatient VTE using validated algorithms. Two-thirds of men with PC had no comorbidity as captured by the Charlson Comorbidity Index. Overall, PC was associated with an approximately 1.7-fold increased risk of VTE compared with the general population (2.2% vs 1.3%) over 5 years of follow-up. To address their main objective, the authors reported the VTE rate ratio by year of follow-up and level of comorbidity. The VTE rate ratio represents the ratio of VTE incidence in the population of interest compared with the incidence in an age-standardized, comorbidity-standardized, and calendar time-standardized control population. To examine specifically whether the effects of PC and comorbidity were simply additive or there was a more complex interaction, the authors used the interaction contrast (IC), a quantitative method of examining the effects of 2 simultaneous exposures (PC, comorbidity) on an outcome (VTE). The approach is well detailed in statistical textbooks.¹⁹ What the authors observed is an apparent interaction between PC and severe comorbidity (Charlson index score ≥ 4 [IC, 4.4; 95% confidence interval, -4.5, 13) (see Ording et al, Table 2¹⁸) and the risk of VTE, whereas there was essentially no interaction between PC and lower levels of comorbidity. The magnitude of the IC was higher in the first year after diagnosis compared with second through fifth years (see Ording et al, Table 2¹⁸).

The study has several strengths, including a well characterized cohort from a rigorous, inclusive national registry; a large sample size; well validated outcomes; use of competing risks to account for increased risk of mortality with PC; and a solid epidemiologic approach to dissecting out possible interaction. And various findings are well supported by prior literature, including an increased risk of VTE in men with PC,⁹ an increased risk of VTE in the first year after surgery,⁸ and an increased risk of VTE with specific comorbidities, such as congestive heart failure and hemiplegia.⁶ However, important limitations need to be kept in mind. First, we lack information on the use of thromboprophylaxis; lower use both in men with PC and in those with greater comorbidity (eg, because of the perceived increased risk of bleeding) could partly

explain the results. Second, the highest risk population was also the smallest (about 2% of PC patients had severe comorbidity), leading to substantial uncertainty around findings. Third, ICs were modestly negative in low and moderate comorbidity settings (see Ording et al, Table 2¹⁸), which is a little counterintuitive; but, again, the confidence intervals are wide. Similarly, the elevated VTE risk in years 2 through 5 after surgery (usually reserved for early stage, nonhigh-risk PC, and usually curative) is a little surprising. Fourth, the median survival between PC cases and controls differed by 1.3 years; and, although men with PC are at slightly higher risk of dying than matched controls, the magnitude is surprising given the excellent 10-year survival with PC in most modern series. These factors lead to questions about the generalizability of the population and some of the findings reported. Fifth, the Charlson Comorbidity Index may be a relatively crude measure of comorbidity in this circumstance, because peptic ulcer disease and congestive heart failure likely do not have the same risk of VTE, yet both are given 1 point on the index. Analyses using specific comorbidities would be more interesting and clinically informative, but sample sizes would constrain any such analyses. Moreover, to the authors' credit, they did provide some data in this regard in Supporting Figure 1. Sixth, it would have been interesting to determine whether rates of fatal VTE were greater among men with PC and comorbidity. The outcome of fatal VTE avoids some of the workup bias associated with a patient who has acute dyspnea and a diagnosis of cancer. Conversely, attribution bias and a much smaller number of events would be potential problems with this approach. Perhaps most important, all of the confidence intervals around the reported ICs included unity: even for the IC that demonstrated an interaction between PC and severe comorbidity.

What are the implications of the authors' findings? Given the above limitations, we are cautious in our interpretation. Although severe comorbidity may interact with PC to increase the risk of VTE, we believe these findings need to be verified in other databases and will likely require even larger samples. At a clinical level, the findings remind us about the need to be vigilant in terms of providing thromboprophylaxis in settings for which there is solid evidence, such as in the postoperative setting and in hospitalized cancer patients.^{6,10} Numerous studies have demonstrated that our quality of care in this arena is not consistently meeting benchmarks (eg, see Cohen et al²⁰). Specific recommendations about pharmacologic and non-pharmacologic thromboprophylaxis, doses, and duration are beyond the scope of this editorial but are well

summarized in guidelines and reviews.^{6,10} Validated risk-prediction models⁶ should be used to ensure that the highest risk individuals are appropriately identified and receive thromboprophylaxis. Finally, if the authors' findings are confirmed, then they may open the door to subsequent trials of more intense and/or longer duration thromboprophylaxis regimens in men with PC and severe comorbidity, although accruing to such studies may be challenging given the nature of the population in question. The findings may also lead to the development of VTE predictive models that integrate PC treatments, comorbidities, and other risk factors. The ability to more precisely determine an individual's risk of VTE during their treatment for PC will allow for better proactive measures, including screening and thromboprophylaxis, to reduce the occurrence and complications from VTE.

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REFERENCES

- Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis [serial online]. *PLoS Med*. 2012;9:e1001275.
- Heit JA. Venous thromboembolism epidemiology: implications for prevention and management. *Semin Thromb Hemost*. 2002;28(suppl 2):3-13.
- Gangireddy C, Rectenwald JR, Upchurch GR, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. *J Vasc Surg*. 2007;45:335-341; discussion 341-332.
- Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med*. 1999;159:445-453.
- Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med*. 2002;162:1245-1248.
- Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e195S-e226S.
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e419S-e494S.
- Cronin-Fenton DP, Sondergaard F, Pedersen LA, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer*. 2010;103:947-953.
- Petterson TM, Marks RS, Ashrani AA, Bailey KR, Heit JA. Risk of site-specific cancer in incident venous thromboembolism: a population-based study. *Thromb Res*. 2015;135:472-478.
- Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25:5490-5505.
- Beyer J, Wessela S, Hakenberg OW, et al. Incidence, risk profile and morphological pattern of venous thromboembolism after prostate cancer surgery. *J Thromb Haemost*. 2009;7:597-604.
- Van Hemelrijck M, Adolffson J, Garmo H, et al. Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. *Lancet Oncol*. 2010;11:450-458.
- Ehdaie B, Atoria CL, Gupta A, et al. Androgen deprivation and thromboembolic events in men with prostate cancer. *Cancer*. 2012;118:3397-3406.
- Tollefson MK, Karnes RJ, Rangel L, Carlson R, Boorjian SA. Blood type, lymphadenectomy and blood transfusion predict venous thromboembolic events following radical prostatectomy with pelvic lymphadenectomy. *J Urol*. 2014;191:646-651.
- Meng MV, Grossfeld GD, Sadetsky N, Mehta SS, Lubeck DP, Carroll PR. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. *Urology*. 2002;60:7-11; discussion 11-12.
- Simone B, De Stefano V, Leoncini E, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetetrahydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *Eur J Epidemiol*. 2013;28:621-647.
- Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. *JAMA*. 2009;301:2472-2485.
- Ording AG, Horvath-Puho E, Lash TL, et al. Prostate cancer, comorbidity, and the risk of venous thromboembolism: a cohort study of 44,035 Danish prostate cancer patients, 1995-2011. *Cancer*. 2015;000:000-000.
- Greenland S, Lash TL, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:71-83.
- Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet*. 2008;371:387-394.