



# Direct Medical Costs Attributable to Cancer-Associated Venous Thromboembolism: A Population-Based Longitudinal Study

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## ABSTRACT

**PURPOSE:** The purpose of this study is to estimate medical costs attributable to venous thromboembolism among patients with active cancer.

**METHODS:** In a population-based cohort study, we used Rochester Epidemiology Project (REP) resources to identify all Olmsted County, Minn. residents with incident venous thromboembolism and active cancer over the 18-year period, 1988-2005 (n = 374). One Olmsted County resident with active cancer without venous thromboembolism was matched to each case on age, sex, cancer diagnosis date, and duration of prior medical history. Subjects were followed forward in REP provider-linked billing data for standardized, inflation-adjusted direct medical costs from 1 year prior to index (venous thromboembolism event date or control-matched date) to the earliest of death, emigration from Olmsted County, or December 31, 2011, with censoring on the shortest follow-up to ensure a similar follow-up duration for each case-control pair. We used generalized linear modeling to predict costs for cases and controls and bootstrapping methods to assess uncertainty and significance of mean adjusted cost differences. Outpatient drug costs were not included in our estimates.

**RESULTS:** Adjusted mean predicted costs were 1.9-fold higher for cases (\$49,351) than for controls (\$26,529) ( $P < .001$ ) from index to up to 5 years post index. Cost differences between cases and controls were greatest within the first 3 months (mean difference = \$13,504) and remained significantly higher from 3 months to 5 years post index (mean difference = \$12,939).

**CONCLUSIONS:** Venous thromboembolism-attributable costs among patients with active cancer contribute a substantial economic burden and are highest from index to 3 months, but may persist for up to 5 years.

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**KEYWORDS:** Active cancer; Cost analysis; Cost of illness; Deep vein thrombosis; Medical care utilization; Pulmonary embolism; Venous thromboembolism

Venous thromboembolism is a common complication of active cancer.<sup>1-3</sup> Active cancer increases venous thromboembolism risk by four- to sevenfold and accounts for nearly 20% of the entire venous thromboembolism burden

occurring in the community.<sup>4,5</sup> In addition, patients with active cancer-associated incident venous thromboembolism are at increased risk for recurrent venous thromboembolism, and survival among cancer patients with incident and

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**Authorship:** All authors had a role in writing the manuscript and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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recurrent venous thromboembolism is significantly reduced.<sup>6-8</sup> Despite the well-established association between cancer and venous thromboembolism,<sup>9-12</sup> there are few data assessing the economic burden of venous thromboembolism in active cancer patients.<sup>13-16</sup> Existing estimates of venous thromboembolism-associated costs among patients with cancer have largely focused on complications of anticoagulation therapy, increased length of hospitalization, and the high frequency of venous thromboembolism recurrence.<sup>13,15,16</sup> Moreover, venous thromboembolism case ascertainment almost always relied on discharge diagnosis codes obtained from billing or administrative claims data.<sup>17</sup> The limitations of discharge diagnosis codes for identifying incident venous thromboembolism are well recognized.<sup>18-21</sup> In addition, information on tumor stage and histologic subtype was not included.<sup>17</sup>

To address these limitations, we performed a population-based cohort study to estimate the medical costs attributable to venous thromboembolism in individuals with active cancer that included the entire spectrum of cancer-associated venous thromboembolism occurring in the community.

## METHODS

### Study Setting and Design

Olmsted County, Minn. (2010 census population = 144,248) provides a unique opportunity for investigating the natural history of venous thromboembolism.<sup>22,23</sup> Under auspices of the Rochester Epidemiology Project (REP), Mayo Clinic, together with Olmsted Medical Center (OMC) (a second group practice), and their affiliated hospitals, provide over 95% of all medical care delivered to local residents, thereby linking the medical records for community residents at the individual level.<sup>24-26</sup> Using REP resources, we performed a cohort study to study cost attributable to venous thromboembolism among cancer patients. The study was approved by the Mayo Clinic and OMC Institutional Review Boards.

### Study Population

All Olmsted County, Minn. residents with incident deep venous thrombosis or pulmonary embolism over the 40-year period, 1966-2005, were identified as previously described.<sup>22</sup> Incident venous thromboembolism events were recorded by experienced nurse abstractors and were

limited to patients residing in Olmsted County for whom this was a first lifetime symptomatic venous thromboembolism.

The present study included all incident venous thromboembolism cases with active cancer (excluding nonmelanoma skin cancer). Active cancer had to have been documented in the 92 days (365/4, or about 3 months) prior to venous thromboembolism event date. Cancer was considered inactive when the patient had undergone curative surgery or chemotherapy or radiotherapy with no evidence of residual disease. Myeloproliferative or myelodysplastic disorders, chronic myelocytic or lymphocytic leukemia, and hematopoietic growth factor therapy for these disorders were considered as always-active cancer. For the few patients with multiple primary cancers, we used the cancer in the 92 days on or prior to the incident venous thromboembolism if one was prior to and one was after venous thromboembolism event. We used

the more recent cancer if both were prior to the venous thromboembolism. If both primary cancers were diagnosed on the same day, a hematologist/oncologist (AAA) re-staged all cancer(s) and we used the cancer with the highest stage.

The Mayo Cancer Registry, available since 1972, includes patient demographics at cancer diagnosis and tumor classification using International Classification of Diseases for Oncology, 3rd edition, and also provides enumeration of the Olmsted County population with cancer from 1973 to the present, from which controls can be sampled.<sup>24</sup> After verifying consent to use of medical records for research and Olmsted County residency, the list of possible cancer controls for each venous thromboembolism case was subset to those Olmsted County residents with cancer whose first cancer diagnosis was within  $\pm 5$  years of the venous thromboembolism case's cancer diagnosis (Figure).<sup>5,27</sup> We further matched on sex, date of birth ( $\pm 5$  years), and year of registration ( $\pm 5$  years). Matching on year of registration ensures a similar duration of medical records. For each case, the list of possible controls was randomly sorted and a control medical visit date after January 1, 1988 was chosen (index date). The control's cancer was confirmed to be active within  $\pm 3$  months of the index date, and the duration of active cancer to be at least as long as or up to 2 years longer than the duration of active cancer of the case. Medical records were also reviewed to confirm no history of venous thromboembolism prior to or within 3 months after the index date.

### CLINICAL SIGNIFICANCE

- Adjusted mean predicted venous thromboembolism-attributable costs among patients with active cancer from index to 5 years post index are substantial.
- Venous thromboembolism-attributable costs were greatest within the 3 months after the event date and remained significantly higher from 3 months to 5 years post index.
- Our findings will inform models that assess the cost-effectiveness of alternative interventions to reduce occurrence and guide reimbursement policy.

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