Long term use of vitamin K antagonists and incidence of cancer: a population-based study

Vittorio Pengo MD,1 Franco Noventa MD,3 Gentian Denas MD,1 Martino F. Pengo MD,4 Umberto Gallo Pharm D,5 Anna Maria Grion Pharm D,5 Sabino Iliceto MD,1 and Paolo Prandoni MD, PhD2

1Department of Cardiothoracic and Vascular Sciences, Division of Clinical Cardiology, University of Padova; 2Thromboembolic Unit, Department of Cardiac Thoracic and Vascular Sciences, 35th and 4th Medical Clinic, Department of Clinical and Experimental Medicine, University of Padova; 5Pharmaceutical Service, District Health Area 16, Padova, Italy

Running head: VKA use and cancer incidence

Correspondence:

Vittorio Pengo MD at the Department of Cardiothoracic and Vascular Sciences, Clinical Cardiology, Thrombosis Centre, University of Padova, School of Medicine

Via Giustiniani 2, 35128 Padova (Italy)

Tel and fax +39 (0) 49 821 5658
e-mail: vittorio.pengo@unipd.it
Abstract

Whether long-term use of vitamin K antagonists (VKA) might affect cancer incidence is a longstanding hypothesis. We conducted a population-based study including all cancer- and thromboembolism-free individuals of our health area; study groups were defined according to chronic anticoagulant use to VKA-exposed and control groups. Cancer incidence and cancer-related and overall mortality was assessed in both groups. 76008 individuals (3231 VKA-exposed and 72777 controls) were followed-up for 8.2 (±3.2) years. After adjusting for age, sex and time-to-event the hazard ratio (HR) of newly diagnosed cancer in the exposed group was 0.88 (95% CI 0.80–0.98; p<0.015). VKA-exposed individuals were less likely to develop prostate cancer, 0.69 (95% CI 0.50–0.97; p=0.008). The adjusted HR for cancer-related and overall mortality was 1.07 (95% CI 0.92–1.24) and 1.12 (95% CI 1.05–1.19), respectively. These results support the hypothesis that anticoagulation might have a protective effect on cancer development, especially prostate cancer.
Introduction
There is evidence that warfarin has an inhibitory effect on tumor growth and metastasis\textsuperscript{1}. Tumor-mediated activation of the haemostatic system has been associated with both tumor stroma formation and metastasis\textsuperscript{2-5}. These findings raise the question of whether using anticoagulant therapies to down-regulate coagulation activation might not only serve to reduce the risk of venous thromboembolism, but also to directly influence cancer cell biology and tumor development. Long-term use of vitamin K antagonists (VKA) has been associated with a lower incidence of cancer, specifically prostate cancer\textsuperscript{6,7}. We conducted a population-based observational cohort study that sought to assess the impact of long-term VKA use (warfarin or acenocoumarol) on the development of newly diagnosed malignancies, and on cancer-related and overall mortality.

Study design
All residents of the Health Area 16 of the Veneto Region (Italy) aged 65 to 90 years in the period January 1, 1996 to December 31, 2002 were included in this study. The Public Health Service system, covering this area, keeps record of all discharge diagnoses from public or private hospitals – using the International Classification of Diseases system codes (ICD-9-CM) – as well as hospital outpatient visits, and medications dispensed – using the Anatomical Therapeutic Chemical (ATC) classification. We identified and excluded from the study all individuals who had ongoing or previous history of neoplastic disease (ICD-9-CM: 140-239), and superficial thrombophlebitis (ICD-9-CM: 451) or venous thromboembolism (ICD-9-CM: 452-453) during the year of enrolment or that before\textsuperscript{8,9}. The period of observation began with the reaching of the 65\textsuperscript{th} birthday during the enrolment period and ended with the reaching of the 90\textsuperscript{th} birthday,
diagnosis of neoplastic disease, death, emigration, or the end of the follow-up period – December 31, 2007 – whichever came first.

VKA exposure was assessed on the basis of ATC codes on the drug prescriptions (ATC code B01AA03 for warfarin and ATC code B01AA07 for acenocoumarol) and used to define the study groups: VKA-exposed and controls. Chronic exposure was evaluated in the 3 years preceding enrollment, and defined as at least 2 prescriptions per year and at least one prescription during the following 2 years. Ascertainment of anticoagulant exposure was validated by randomly extracting a sample of 300 individuals (∼1%) from the exposed group and reviewing their medical records, phone interview of the individuals or their caregivers.

The endpoints of the study were the incidence of previously undiagnosed malignancies identified at the three-digit coding level of the ICD-9-CM, and overall and cancer-related mortality.

The study was approved by the Veneto Region privacy and data-protection board and by the Local Ethics Committee.

The incidence of cancer is expressed per 1000 individuals. The predicted proportion of cancer incidence in the exposed group was calculated by applying the observed proportion in the control group. The difference between the number of expected and observed cancers was expressed as avoided cancers.

We used Koopman’s approximate method to compute cancer development, total and cancer-related mortality relative risk (RR) and their associated 95%CI.

Cox proportional-hazards regression analysis was used to estimate hazard ratio (HR) of cancer development adjusted for age at enrollment (as continuous variable), sex and time to event. Data analysis was performed using SPSS version 18.0 (SPSS, Inc., Chicago IL).
Results and discussion

Of the 89787 eligible individuals, 13779 were excluded because they had been diagnosed with cancer or suffered superficial thrombophlebitis or venous thromboembolism during the year of entry or that before, died or moved during the year of enrollment or thereafter. Of the remaining cohort, 3231 were included in the VKA-exposed group, 72777 served as controls. After validation of the medical records, 94% of the patients were found to be correctly included in the exposed group. The individuals in the VKA-exposed group were significantly older (76.4±6.8 vs 74.8±7.2), and followed-up for a longer time (9.1±2.4 years vs 8.8±2.6 years); there were more females on both groups (50.4% on the VKA-exposed and 59.9% on the control group). During follow up, 421 new malignancies were recorded among the VKA-exposed individuals (130/1000), and 9741 among the control individuals (134/1000), yielding a crude RR of 0.97 (95% CI 0.88–1.06). After adjusting for age and sex (Figure 1), the incidence of cancer was significantly lower in the VKA-exposed individuals (HR=0.88; 95% CI 0.80–0.98; p<0.015). Among specific tumors (Table 1), the incidence of prostate cancer was significantly reduced in the exposed group, 0.69 (95% CI 0.50–0.97; p=0.008).

Overall, during the follow up period, there were 1023 deaths (317/1000) among the VKA-exposed individuals and 15349 (211/1000) among controls (crude RR 1.50; 95% CI 1.42–1.58). Age and sex adjusted mortality was higher among the VKA-exposed individuals (HR=1.12; 95% CI 1.05–1.19). Among the newly diagnosed malignancies, 184 deaths (437/1000) were recorded in the VKA-exposed group and 3683 among the controls (378/1000), yielding a crude RR of 1.16 (95% CI, 1.03 to 1.29). Age and sex adjusted mortality was similar in both groups (HR=1.07; 95% CI 0.92–1.24).
These results support the proposed hypothesis that chronic VKA use has a protective role on cancer incidence. Among specific cancer types, statistical significance was reached for prostate cancer only. Proposed mechanisms for this antineoplastic effect involve thrombin relation to protease activated receptors (PARs), GAS6 and AXL.\textsuperscript{11-13} GAS6/AXL axis in turn regulates prostate cancer invasion, proliferation, and survival.\textsuperscript{14} Coumarin given to rats bearing the R-3327H prostate adenocarcinoma decreased the size of the primary tumor.\textsuperscript{15} The possible protective role of chronic oral anticoagulation was assessed in human studies\textsuperscript{16-18} with favorable results; although the validity can be questionable due to the low number of the events recorded. Some studies\textsuperscript{6, 7} support the hypothesis that chronic anticoagulation has a protective effect on cancer incidence, especially on prostate cancer. The fact that a reduced risk of cancer was observed years after exposure suggests a probable protective effect of warfarin at the stage of tumor initiation or promotion rather than an effect on an established tumor.

Other studies found no significant difference in urogenital cancer incidence between warfarin users and non-users, although the increased risk of cancer in smokers might have overweighed any potential benefit of warfarin in one study\textsuperscript{19}, while the short follow-up period might have influenced the results on the other.\textsuperscript{20}

Although retrospective, this is a large population-based study with long follow-up. Selection bias in our study is unlikely: first, our cohort included all residents; second, because cancers were identified through the Public Health System database, it is difficult that events might have been overlooked; third, recall bias in terms of exposure to VKA could hardly occur since the computerized approach was validated in 300 randomly extracted patients.

A potential limitation of this study is that other important risk factors for neoplastic diseases such as changes in diet, decrease in alcohol consumption, smoking cessation,
more frequent medical visits, could not be taken into consideration. However, because the whole population of the Area was included, these factors were probably balanced between the groups.

In conclusion, our results support the hypothesis that chronic VKA exposure has a protective role on cancer incidence – especially prostate cancer – in individuals of 65 years or older. Other large-scale prospective, long follow-up studies are needed to confirm these results.

**Author Contributions**

V.P., F.N., and P.P. planned the study and contributed to the writing of the manuscript; G.D., M.F.P., U.G., A.M.G. managed the study database and analyzed the data. S.I. organized the study. All authors critically reviewed the article and approved the final version.

**Disclosures**

The authors have nothing to disclose.

This study has been presented as abstract at the XXII Congress of the ISTH, 2009.
References


Table 1. Risk ratios of specific cancer types among VKA-treated patients and control population

<table>
<thead>
<tr>
<th>Site or type of cancer (ICD9-CM code)</th>
<th>Cancer Risk Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
</tr>
<tr>
<td></td>
<td>Controls (72777)</td>
</tr>
<tr>
<td>Upper gastrointestinal (140-145,146-149,150-151)</td>
<td>504</td>
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<tr>
<td>Lower gastrointestinal (152-154)</td>
<td>1454</td>
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<tr>
<td>Liver, gallbladder (155-156)</td>
<td>364</td>
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<tr>
<td>Pancreatic (157)</td>
<td>238</td>
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<tr>
<td>Respiratory tract (160-162)</td>
<td>1004</td>
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<tr>
<td>Skin cancer including melanoma (172-173)</td>
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<tr>
<td>Breast (174-175)</td>
<td>1146</td>
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<tr>
<td>Uterus and other female reproductive (in 45237 female) (179-184)</td>
<td>304</td>
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<tr>
<td>Renal and urinary tract (188-189)</td>
<td>1189</td>
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<td>Prostate (in 30771 male) (185)</td>
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<td>Leukemia and other blood (200-208)</td>
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<tr>
<td>Other (158-159,163-165,170-171,176,186-187,190-195,199)</td>
<td>528</td>
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<tr>
<td>Metastatic disease (196-198)</td>
<td>1354</td>
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<tr>
<td>Any cancer (140-208)</td>
<td>9741</td>
</tr>
</tbody>
</table>

* statistically significant difference

Abbreviations: RR, relative risk; HR, hazard ratio.
Figure Legends

Figure 1. Incidence of cancer in VKA-exposed individuals (dotted line) and in controls (continuous line) during follow-up (HR=0.88; p=0.015).
Figure 1.
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