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Original Article

Cancer, other comorbidity, and risk of venous thromboembolism after stroke: a population-based cohort study☆

Priscila Corraini, PhD [a,*], Anne Gulbech Ording, PhD [a], Victor W. Henderson, MD [a,b,c], Szimonetta Szépligeti, MSc [a], Erzsébet Horváth-Puhó, PhD [a], Henrik Toft Sørensen, DrMedSc [a,c]

[a] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Neurology & Neurological Sciences, Stanford University, Stanford, California, USA
[c] Department of Health Research & Policy (Epidemiology), Stanford University, Stanford, California, USA

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ABSTRACT

Introduction: The impact of cancer and other comorbidity on the risk of venous thromboembolism (VTE) after stroke is poorly understood.
Methods: We used Danish population-based national databases to conduct a cohort study encompassing 201,025 patients diagnosed with a first-time ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage or unspecified stroke between 1995 and 2012. As a comparison cohort, 983,222 members of the general population were matched to the stroke patients by date of diagnosis, year of birth, sex, and specific comorbidities, using conditions in the Charlson Comorbidity Index and other VTE risk factors. We computed VTE cumulative risks, rates, and rate ratios. We examined the interaction with comorbidity, defined as the excess VTE rates not explained by stroke and comorbidity alone, for up to five years following stroke.
Results: Five-year VTE risks were 2.1% and 1.9% in the stroke and comparison cohorts, respectively. Three-month VTE rates peaked at a 5-fold increase (95% confidence interval [CI]: 4.4; 5.2) in stroke patients and remained 13% to 43% increased relative to the general population during subsequent follow-up. During the first three months after stroke, 15% to 33% of the VTE rates were attributable to the interaction between stroke and moderate (2-3) to high (≥4) comorbidity based on Charlson Comorbidity Index scores. Non-metastatic solid tumors and metastatic disease accounted for most observed interaction with stroke, representing 41% and 56% of attributable three-month VTE rates, respectively. No such interaction between comorbidity and stroke was observed during subsequent follow-up.
Conclusions: Comorbidity, particularly cancer, increased the risk of VTE within three months following stroke.

1. Introduction

Stroke is a major cause of death worldwide [1]. Among stroke survivors, acute complications such as pneumonia, urinary tract infections, and falls are common even in specialized stroke units [2,3]. Venous thromboembolism (VTE) is a less common complication during stroke hospitalization (< 8%) [2,4–7], though it is potentially life-threatening [5,7] and is usually preventable.

In a case-control study of approximately 6,000 VTE patients and their controls [8], VTE cases were four times more likely to have had a stroke within 3 months before the VTE diagnosis. However, the excess risk of VTE in stroke patients compared to the general population is unknown. As most stroke patients are over age 60 at diagnosis [9], comorbidity is likely common. Cancer, obesity, and cardiovascular diseases are shared risk factors for stroke and VTE [1,10–12]. If the excess risk of VTE among stroke patients with comorbidities is higher than that explained by comorbidity and stroke alone in a particular period, VTE-prophylaxis recommendations might be tailored to stroke patients with comorbidities.

VTE risks after stroke have not been reported beyond hospitalization [2,4–7,13,14], and previous studies have largely focused on ischemic stroke [5,6,13]. Improving strategies for VTE prevention in stroke patients post-hospitalization may reduce morbidity and improve survival.

In a nationwide population-based cohort study we examined the risk of VTE in first-time ischemic and hemorrhagic stroke patients, as well as the excess risk of VTE in these patients, compared to a matched general population cohort, for up to five years after a stroke diagnosis. We examined VTE risk in the stroke and general population cohorts to assess the impact of comorbidity on risk of VTE in stroke patients, as a measure of excess VTE rates not explained by the additive effects of stroke and comorbidity.

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* Corresponding author at: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200, Aarhus, N, Denmark.
E-mail address: priscilacorraini@gmail.com (P. Corraini).

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2. Materials and Methods

2.1. Design, setting, and data sources

We used Danish nationwide medical databases to conduct a population-based cohort study of patients ≥ 18 years of age diagnosed with acute strokes during 1995-2012 (Danish Data Protection Agency approval no.1-16-02-1-08). The Danish healthcare system provides all residents with tax-supported free access to healthcare. The Danish National Patient Registry (DNPR) has recorded >99% of all hospitalizations since 1977 and hospital outpatient and emergency room visits since 1995 [15]. The DNPR contains information on dates of inpatient admission, discharge, and outpatient clinic visits. One primary discharge diagnosis, which represents the main reason for hospitalization, and optional secondary diagnoses are coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until 1993 and *Tenth Revision* (ICD-10) thereafter. Since 2000 the DNPR also has recorded information on computed tomography and magnetic resonance brain imaging. Since 1968, the Danish Civil Registration System (CRS) has assigned a unique registration number to all Danish residents at birth or upon immigration [16], allowing unambiguous linkage among databases. The CRS also maintains up-to-date information on migration and vital status of the entire Danish population, allowing for nearly complete follow-up.

2.2. Stroke cohort

We used the DNPR to identify all inpatients ≥ 18 years of age with a first-ever diagnosis of ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage or unspecified stroke, based on ICD-10 codes (Table A1). We included only stroke patients confirmed during inpatient hospitalization, due to the relatively higher reported misclassification frequency in the DNPR of strokes diagnosed from emergency departments [17]. We also used DNPR records back to 1977 to exclude patients with any previous diagnosis of stroke, other cerebrovascular disease or hemiplegia (as a proxy for previous stroke) as of the date of stroke diagnosis (defined as the index date).

2.3. General population comparison cohort

To construct a comparison cohort, we used the CRS and DNPR to identify for each stroke patient up to five individuals from the general population without a record of stroke, other cerebrovascular disease, or hemiplegia as of the index date. Each member of the comparison cohort was matched to a stroke patient by sex, year of birth in 5-year intervals, and history of individual comorbidities diagnosed within ten years before the index date.

2.4. Comorbidity

We identified comorbidity using outpatient and inpatient diagnoses in the DNPR of all 19 conditions included in the Charlson Comorbidity Index (CCI), except for cerebrovascular disease and hemiplegia [18]. Compared with medical records, the positive predictive value of conditions in the DNPR included in the CCI is 98% [19]. Each CCI condition has a severity-weight score between one and six based on their adjusted one-year mortality [18,19]. In the current study, comorbidities were assessed individually and also as components of a summed severity-weighted CCI score. We added atrial fibrillation/flutter [10], obesity [11], and inflammatory bowel disease [20] as comorbidities to the CCI score due to their potential association with VTE and stroke, assigning a severity-weighted score of one [21]. Individuals were categorized according to their summed severity-weighted score on the augmented CCI as 0 (no comorbidity), 1 (low comorbidity), 2-3 (moderate comorbidity), or ≥4 (high comorbidity).

2.5. Venous thromboembolism

We identified VTE in the DNPR as any inpatient or outpatient clinic discharge diagnosis of pulmonary embolism (PE), deep venous thrombosis (DVT), or other VTE diagnosis. We excluded VTEs registered solely at emergency departments because they frequently represent working diagnoses, with low diagnostic accuracy [22]. We also made an effort to distinguish VTE events which were associated to or not to established classical risk factors for VTE. We considered the following established VTE risk factors: an inpatient or outpatient diagnosis of cancer at any time before the VTE; or fracture or trauma, surgery, infection, pregnancy or delivery, or prolonged hospital immobilization within 90 days before the VTE diagnosis. We defined prolonged immobilization as an inpatient stay lasting seven days or more from admission to discharge or death [23]. If a patient was transferred between hospital units, days spent in all units were considered as a single hospitalization [24]. Patients diagnosed with both PE and DVT or other VTE on the same discharge date were classified as having PE due to its higher impact on mortality. Similarly, patients diagnosed with both DVT and other VTE were classified as having DVT.

2.6. Follow-up

Follow-up started on the index date and continued until VTE, death, emigration, five years, or December 31, 2012, whichever occurred first. We ascertained vital status and emigration using the CRS [16]. If a comparison cohort member was diagnosed with stroke, follow-up was censored on the stroke date. The affected individual then was enrolled in the stroke cohort and matched with up to five new stroke-free members of the general population.

2.7. Statistical analysis

We computed cumulative VTE risk and incidence curves for the stroke (ischemic and hemorrhagic) and general population comparison cohorts, considering death as a competing risk [25]. We also computed the VTE rate per 1,000 person-years for events overall and separately for PE, DVT, and other VTEs, as well as for VTEs associated with established classical risk factors and other types of VTE. We stratified follow-up time to calculate VTE rates for three periods: 0-3 months, >3-12 months, and >1-5 years after the index date. This also allowed us to assess VTE incidence for those alive and free of VTE up to the 3rd and 12th month after stroke diagnosis. For this purpose, we dissolved the matching and standardized the rates to the age and sex distribution of stroke cohort members as of their index dates. Based on standardized VTE rates, we assessed the interaction between stroke and comorbidity using interaction contrasts and 95% confidence intervals (CIs) [26]. The interaction contrast is a measure of excess VTE risk in patients with both stroke and comorbidity, beyond that expected by the sum of their independent effects [26]. To further examine the stroke patient benefit from tailoring VTE strategies among those with comorbidity, we calculated the attributable fraction due to interaction. The attributable fraction captured the proportion (%) of the VTE rate among individuals doubly exposed to stroke and comorbidity attributed to exposure interaction [27,28]. The method for calculating interaction contrasts and its associated attributable fraction is detailed in the Appendix.

We used Cox proportional hazard regression to compute hazard ratios (HRs) as a measure of VTE rate ratios within the categories of the augmented CCI. The proportionality assumption was confirmed for the three follow-up periods using log-log plots. We stratified VTE rates and interaction contrasts in stroke patients with specific diagnosis by type of stroke (ischemic *vs* hemorrhagic). We performed sensitivity analyses restricted to 2004-2012 to reflect more widespread dissemination of thrombolytic therapy, other VTE prophylactic measures, and diagnosis with advanced auxiliary brain imaging in stroke patients during this later period. Other sensitivity analyses were restricted to stroke patients who had: (1) primary stroke diagnoses and (2) brain imaging