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Cardiovascular Diseases and the Risk of Venous Thromboembolism: A Hospital-based Case-control Study

Chen-Chang Yang[1,2]*, Chih-Chin Kao[2]

[1]*Department of Environmental and Occupational Medicine, National Yang-Ming University School of Medicine, and* [2]*Division of Clinical Toxicology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C.*

Background: The effects of various cardiovascular diseases on the risk of venous thromboembolism (VTE) are not well defined. To gather more information, we performed a hospital-based case-control study to evaluate the effects of major cardiovascular diseases on the risk of VTE.

Methods: We identified all incident cases of VTE needing hospitalization and anticoagulant therapy between January 1990 and December 2002 in a large tertiary hospital. Each case was matched with up to 4 controls, randomly selected from inpatients who were not hospitalized due to any of the exposures, on age, sex, calendar time and veteran/nonveteran status.

Results: This study comprised 173 cases of VTE and 546 matched controls. The adjusted odds ratio (OR) of VTE was significant among patients with peripheral atherosclerotic diseases (OR 7.1, 95% confidence interval [CI] 1.4–34.4), and nondebilitating cerebrovascular diseases (OR 2.5, 95% CI 1.4–4.7). Other independent risk factors for VTE included a body mass index $\geq 25.0\ kg/m^2$, current estrogen use, a history of hyperlipidemia and varicose veins.

Conclusion: Peripheral atherosclerotic disease and nondebilitating cerebrovascular disease are important risk factors for VTE. Patients with these diseases should therefore be frequently evaluated for the possible coexistence of VTE and, if appropriate, should be given prophylaxis. Failure to take into account the potential confounding effects of these diseases may also result in an erroneous estimate of the effect of drug exposures on the risk of idiopathic VTE. [*J Chin Med Assoc* 2007;70(3):103–109]

Key Words: cardiovascular disease, confounding factors, pulmonary embolism, venous thrombosis

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a potentially fatal disease. To reduce the incidence and mortality of VTE, it is important to identify those patients who are at risk and give them appropriate prophylactic therapy. Numerous studies have attempted to identify or define the risk factors of VTE; however, the results are inconclusive.[1–7] It is especially uncertain whether there is a link between coronary heart disease and/or other cardiovascular diseases and VTE. In the study of "idiopathic" VTE, some researchers excluded various cardiovascular diseases because they believed that patients with preexisting cardiovascular diseases were likely to be less healthy and might be less mobile;[8–10] while other researchers did not completely agree with this.[11,12] For example, in the trial—Heart and Estrogen/progestin Replacement Study, which was designed to study the association between postmenopausal hormone therapy and recurrent cardiovascular events, Grady et al found that the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), but not other lipid-lowering drugs, reduced the risk of idiopathic VTE, which was defined in their study as women who did not have concomitant cancer, fatal myocardial infarction, congestive heart failure, or stroke, and who did not have a fracture, inpatient surgery, or hospitalization

*Correspondence to: Dr Chen-Chang Yang, Division of Clinical Toxicology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: ccyang@vghtpe.gov.tw • Received: May 2, 2006 • Accepted: December 22, 2006

within the 3 months prior to the development of the VTE event.[11] The authors postulated that the favorable mechanisms for statins on arterial thrombus formation might also decrease the risk of VTE among patients with preexisting coronary heart disease.[13] However, the incidence of idiopathic VTE in the placebo group in the trial was substantially higher than the previously reported incidence of "idiopathic" VTE in studies that excluded coronary heart disease.[9,14] Another 2 studies that did not completely exclude patients with preexisting cardiovascular diseases also suggested a possible beneficial effect of statins on VTE.[12,15] Nevertheless, Yang et al, in a study of statins and "idiopathic" VTE, excluded patients with major cardiovascular diseases from the study population and did not find an inverse association between statin use and the risk of idiopathic VTE.[10] The somewhat contradictory findings between the aforementioned studies highlight the need to better delineate the role of coronary heart disease and/or other major cardiovascular diseases in the development of VTE.

An association between major cardiovascular diseases and VTE, if present, would be of major clinical importance since the prevalence of these diseases is high and since it is important to exclude these diseases when designing epidemiologic studies comparing the effect of various drug exposures on the risk of VTE. To provide more information on this issue, we conducted a hospital-based, case-control study to evaluate the relation between major cardiovascular diseases and the risk of VTE.

Methods

Data source and study population

The study was conducted using the inpatient records of Taipei Veterans General Hospital from January 1, 1990 to December 31, 2002. Taipei Veterans General Hospital, a medical center located in Taipei, Taiwan, was originally founded in 1959 to serve the veterans of the country. Nevertheless, the hospital has gradually expanded to become one of the largest tertiary medical centers in Taiwan, and currently serves both veterans and nonveterans. By the year 2006, Taipei Veterans General Hospital had 2,901 beds and the average number of hospital admissions exceeded 75,000 per year during the study period.

Case definition and control selection

Using an automated computer search of specific *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9CM) codes for deep vein thrombosis and pulmonary embolism (codes 415.1, 415.19, 451.1, 451.11, 451.19, 451.2, 451.81, 453.2, 453.8, 453.9 and V12.51), we identified 1,760 subjects who were discharged from the hospital with a diagnosis of VTE during the study period. We then reviewed the records of a random sample of 100 patients to find a more efficient algorithm for case identification. Based on the information gained from this review, we excluded 972 patients from further study using available computerized information.

The medical records of 11 of the remaining 788 potentially eligible patients were not available for review, thus a total of 777 patients' records were reviewed by both investigators to ascertain their case status. The date of first hospital admission for VTE was defined as the index date. Patients were considered to have incident VTE if they were hospitalized with a first-time diagnosis of VTE and received anticoagulant therapy thereafter. A diagnosis of deep vein thrombosis had to be confirmed by venogram, ultrasound or Doppler scan; and pulmonary embolism by ventilation perfusion scan, angiograpy, or computed tomography. In addition, patients who had active cancer (excluding nonmelanoma skin cancer), coagulopathies, vasculitis, chronic renal diseases, alcohol-related diseases, drug abuse, psychotic disorders, epilepsy, cystic fibrosis, New York Heart Association (NYHA) class III and IV heart failure, or stroke with lower extremity paralysis or marked paresis prior to the index date were excluded. Patients who had major surgery (e.g. abdominal surgery or hip replacement), trauma (e.g. motor vehicle accident), fracture, immobilization, or hospitalization within the 3 months prior to the development of VTE were also excluded. Further, patients who developed VTE during pregnancy, 3 months postpartum, or hospital admission, were also excluded. Any disagreement about case status between the 2 reviewers was resolved by consensus.

Potential controls were those patients who were admitted to the hospital's ophthalmology, ear/nose/throat and dermatology departments with a diagnosis unrelated to cardiovascular diseases during the study period, and who did not have a diagnosis of VTE before the index date. For each case, up to 4 controls were randomly selected from the computer registry and were matched to the case on age (within 5 years), sex, index date (within 10 days of the same index date as for cases) and veteran/nonveteran status. The medical records of all controls were reviewed to confirm that the controls were alive at the index date and did not have any of the exclusion criteria applied to the cases. To avoid potential differences in the referral patterns between the cases and the controls, all study subjects should

have had at least 1 visit to other departments of the study hospital in the year prior to the index date, except for patients who did not have any major systemic illness.

Exposures of interest and potential confounders

Information on exposures of interest (major cardiovascular diseases) was assessed from the hospital records. The diagnoses of various exposures were supported both by the medical records and relevant clinical findings, such as repetitive blood pressure measurements, computed tomography of the brain, coronary angiography and limb Doppler scan. In addition to the exposures, we also evaluated the following potential confounders: smoking (none, current, ex-smoker); body mass index (<23, 23–24.9, ≥ 25 kg/m^2, unknown); aspirin use (none, current, past); lipid-lowering drug use; hormone replacement therapy or oral contraceptive use (none, current, past); chronic nonalcoholic liver disease (e.g. mild cirrhosis); atrial fibrillation; diabetes mellitus; hyperlipidemia; and varicose vein. Current aspirin exposure was defined as a prescription for aspirin within 3 months prior to the index date; and past use, more than 3 months. Lipid-lowering drugs were grouped into statins, fibrates, other lipid-lowering drugs, mixed use (use of ≥ 2 drug classes concomitantly) and nonuse. Exposure timing of lipid-lowering drugs was further categorized as current, recent and past use. Current use was defined as having had the last prescription of a lipid-lowering drug ≤ 45 days prior to the index date; recent use, 46–90 days; and past use, ≥ 91 days. Women were classified as current users of hormone replacement therapy or oral contraceptives if they had received any relevant prescription within the 6 months prior to the index date, and past users if they had stopped treatment more than 6 months before the index date.

Statistical analysis

We used conditional logistic regression analysis to explore the association between various cardiovascular diseases and the risk of having VTE. All variables that had a $p \leq 0.20$ in univariate analyses were entered into the multivariate model, and a stepwise procedure was used to eliminate variables other than exposures that became insignificant. Relative risks were estimated by OR and were calculated using patients without individual cardiovascular disease as the reference group. We further conducted subgroup analyses on age, sex and veteran/nonveteran status. All of the above analyses were performed using STATA 8.0 software. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). The p values are 2-sided.

Results

After excluding 2 cases without matched controls, a total of 173 cases (including 140 cases with deep vein thrombosis, 29 cases with pulmonary embolism and 4 cases with both) and 546 controls were identified from the hospital records. The mean age was 66.2 ± 9.8 years for the case patients and 66.5 ± 9.9 years for the controls. Men outnumbered women in the study. Cases and controls differed on many baseline characteristics, including body mass index, hormone therapy, aspirin use, history of chronic nonalcoholic liver disease, hyperlipidemia and varicose veins (Table 1). Table 1 also presents the results of multivariate analysis. After adjusting for major cardiovascular diseases, cases were more likely than controls to be current estrogen users, to have a body mass index ≥ 25 kg/m^2, and to have preexisting hyperlipidemia and varicose veins. In the aforementioned analyses, we combined current and recent lipid-lowering drug exposures, statin and mixed lipid-lowering drug use and all nonstatin lipid-lowering drug use because there was only 1 case with recent lipid-lowering drug exposure, 1 case with mixed lipid-lowering drug use and 1 control with nonstatin, nonfibrate lipid-lowering drug use.

Table 2 summarizes the association between various major cardiovascular diseases and the risk of VTE. Using patients without specific cardiovascular disease of study interest as the reference group, cases were more likely to have preexisting hypertension, peripheral atherosclerotic disease, NYHA class I and II heart failure and nondebilitating cerebrovascular disease than controls.

A history of peripheral atherosclerotic disease (OR 7.1, 95% CI 1.4–34.4) and nondebilitating cerebrovascular disease (OR 2.5, 95% CI 1.4–4.7) remained statistically significant after controlling for other baseline characteristics (Table 2). There was no effect modification by age, sex and veteran/nonveteran status (data not shown).

Discussion

The findings of this hospital-based case-control study including 173 VTE cases and 546 control patients indicate that peripheral atherosclerotic disease and nondebilitating cerebrovascular disease are associated with a higher risk of VTE. This study also showed an association between the risk of VTE and current estrogen use, body mass index ≥ 25 kg/m^2, hyperlipidemia and varicose veins.

Table 1. Characteristics of case ($n = 173$) and control ($n = 546$) patients and their association with the risk of venous thromboembolism

Characteristics	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p*
Age (yr)					
36–50	18 (10.4)	56 (10.3)	–	–	–
51–65	45 (26.0)	134 (24.5)	–	–	–
66–80	110 (63.6)	356 (65.2)	–	–	–
Sex (Male)	122 (70.5)	394 (72.2)	–	–	–
Smoking					
None	108 (62.4)	360 (65.9)	–	–	–
Current	36 (20.8)	121 (22.2)	1.0 (0.6, 1.6)	–	–
Ex-smoker	29 (16.8)	65 (11.9)	1.5 (0.9, 2.6)	–	–
Body mass index (kg/m^2)					
< 23.0	34 (19.7)	166 (30.4)	–	–	–
23.0–24.9	36 (20.8)	133 (24.4)	1.4 (0.8, 2.4)	1.5 (0.8, 2.7)	0.222
≥ 25.0	84 (48.6)	236 (43.2)	1.7 (1.1, 2.8)	1.8 (1.1, 3.1)	0.025
Unknown	19 (11.0)	11 (2.0)	7.5 (3.3, 17.2)	6.5 (2.6, 16.7)	< 0.001
Estrogen use					
None	157 (90.8)	535 (98.0)	–	–	–
Current	13 (7.5)	6 (1.1)	9.5 (3.0, 29.9)	10.4 (2.8, 39.2)	0.001
Past	3 (1.7)	5 (0.9)	2.6 (0.5, 13.7)	2.8 (0.4, 17.2)	0.276
Aspirin use					
None	139 (80.4)	464 (85.0)	–	–	–
Current	20 (11.6)	60 (11.0)	1.2 (0.7, 2.1)	–	–
Past	14 (8.1)	22 (4.0)	2.6 (1.2, 5.6)	–	–
Lipid-lowering drugs					
Nonuse	166 (96.0)	531 (97.3)	–	–	–
Current statin use	4 (2.3)	6 (1.1)	2.1 (0.5, 9.0)	–	–
Past statin use	1 (0.6)	4 (0.7)	0.8 (0.1, 7.3)	–	–
Current nonstatin use	1 (0.6)	1 (0.2)	3.5 (0.2, 55.8)	–	–
Past nonstatin use	1 (0.6)	4 (0.7)	0.8 (0.1, 7.1)	–	–
Chronic nonalcoholic liver disease					
No	173 (100.0)	539 (98.7)	–	–	–
Yes	0 (0.0)	7 (1.3)	–	–	–
Atrial fibrillation					
No	168 (97.1)	541 (99.1)	–	–	–
Yes	5 (2.9)	5 (0.9)	2.9 (0.8, 10.2)	–	–
Diabetes mellitus					
No	143 (82.7)	457 (83.7)	–	–	–
Yes	30 (17.3)	89 (16.3)	1.1 (0.7, 1.8)	–	–
Hyperlipidemia					
No	135 (78.0)	500 (91.6)	–	–	–
Yes	38 (22.0)	46 (8.4)	3.4 (2.0, 5.7)	2.9 (1.6, 5.2)	< 0.001
Varicose vein					
No	153 (88.4)	535 (98.0)	–	–	–
Yes	20 (11.6)	11 (2.0)	6.1 (2.7, 13.5)	5.6 (2.3, 13.8)	< 0.001

**Adjusted for matching factors (age, sex, index date, veteran/nonveteran status) and major cardiovascular diseases. OR = odds ratio; CI = confidence interval.*

Many physical illnesses predict the occurrence of VTE[1–7] and may confound the association between the exposures of interest and VTE if they are also related to the exposures. Studies on "idiopathic" VTE therefore should exclude patients with clinical risk factors of VTE so that the strong effect of risk factors will not mask or confound the effect of the exposure(s) being assessed. Recent trauma, fracture, major surgery, hospitalization,

Table 2. Association between major cardiovascular diseases and the risk of venous thromboembolism in case ($n = 173$) and control ($n = 546$) patients in both univariate and multivariate analyses

Characteristics	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p*
Hypertension					
No	99 (57.2)	360 (65.9)	–	–	–
Yes	74 (42.8)	186 (34.1)	1.5 (1.0, 2.2)	1.1 (0.7, 1.8)	0.552
New York Heart Association class I and II congestive heart failure					
No	164 (94.8)	539 (98.7)	–	–	–
Yes	9 (5.2)	7 (1.3)	3.7 (1.4, 9.9)	2.3 (0.7, 7.4)	0.179
Peripheral atherosclerotic disease					
No	166 (96.0)	543 (99.5)	–	–	–
Yes	7 (4.1)	3 (0.5)	7.6 (1.9, 29.5)	7.1 (1.4, 34.4)	0.016
Nondebilitating cerebrovascular disease					
No	143 (82.7)	508 (93.0)	–	–	–
Yes	30 (17.3)	38 (7.0)	2.8 (1.6, 4.7)	2.5 (1.4, 4.7)	0.003
Coronary heart disease					
No	148 (85.6)	492 (90.1)	–	–	–
Yes	25 (14.5)	54 (9.9)	1.5 (0.9, 2.4)	1.2 (0.6, 2.1)	0.610

**Adjusted for matching factors (age, sex, index date, veteran/nonveteran status) and baseline characteristics (body mass index, estrogen use, hyperlipidemia, varicose veins). OR = odds ratio; CI = confidence interval.*

cancer, coagulation disorders, severe congestive heart failure, stroke with marked lower extremity weakness, pregnancy and past history of VTE are thus generally excluded in the study of idiopathic VTE.[8–11,15–17] The effects of other diseases, especially certain major cardiovascular diseases (e.g. coronary heart disease), on VTE, however, are less clearly defined.

Diseases that immobilize or paralyze the lower limbs are expected to be associated with the risk of VTE since venous stasis is of major importance in the formation of venous thrombosis.[3] Such a concept is supported by the consistent observations of more frequent VTE events among patients with diverse causes of limb inactivity, such as trauma, surgery and hospitalization.[1,3,6] Similarly, patients with severe congestive heart failure, symptomatic peripheral atherosclerotic diseases and cerebrovascular diseases are likely to be less mobile due to decreased cardiac output, limiting claudication and limb paresis. In this study, we excluded patients with NYHA class III and IV heart failure, and stroke patients with marked lower extremity weakness because these 2 conditions are well-defined risk factors for VTE.[3] Nevertheless, we found that there remained a positive association between peripheral atherosclerotic diseases and nondebilitating cerebrovascular diseases and the risk of VTE. Previous studies had shown that peripheral atherosclerotic diseases and cerebrovascular diseases might be independent risk factors for VTE, and patients with more severe diseases were associated with a higher risk of VTE.[1,18–20] In this study, most patients with peripheral atherosclerotic diseases and/or cerebrovascular diseases were symptomatic. Our findings thus support the significant role of venous stasis in the etiology of VTE and indicate that even mild, nondebilitating lower limb paresis could increase the risk of VTE.

Also, varicose vein had been linked with the risk of VTE.[1,3,16] Heit et al, in a case-control study, found that the risk of VTE related to varicose vein varied by age, with higher risk among patients who were younger.[1] In the World Health Organization study of combined oral contraceptives and VTE, a history of varicose vein was identified as a risk factor for VTE as well.[16] Although such an association was not consistently observed across studies,[1,16,17] the pathophysiology of varicose vein is related to congenital and/or acquired abnormalities of the deep venous system.[21] Further, patients with varicose vein may suffer from venous stasis and ulcer, which can lead to less physical activity.[22] Varicose veins may also be complicated with superficial vein thrombosis, an independent risk factor for VTE.[23]

Hyperlipidemia, especially hypercholesterolemia, has been linked to the risk of VTE in some previous studies.[24,25] It was postulated that hyperlipidemia might directly affect the venous wall or cause progressive

vascular derangement through impaired fibrinolysis.[23] Although the exact pathophysiologic mechanisms of hyperlipidemia-related VTE remain undefined, our findings on the association between hyperlipidemia and VTE support the above proposition. Further studies are needed to better understand the role of hyperlipidemia in the development of VTE.

Hospital-based case-control studies have advantages and disadvantages. One advantage of this study was the complete identification of all case patients in the study hospital and the easy accessibility of relevant medical records. All cases were carefully reviewed and were unlikely to be misclassified because objective diagnostic tests of VTE were required for the diagnosis. The information on the exposures was also likely to be complete and accurate since we studied coronary heart disease and other major cardiovascular diseases, which were routinely recorded in the hospital records. Moreover, we employed various objective diagnostic tests in the ascertainment of the exposures.

The random identification of controls from patients who were not hospitalized due to any of the exposures and the application of similar exclusion criteria to both the case and the control patients precluded selection bias in the controls. Further, because we studied confirmed VTE cases who needed hospitalization and anticoagulant therapy, and physicians were not aware of any association between major cardiovascular disease and the risk of VTE during the study period, referral or diagnostic bias should be minimal, if any.

Many physical illnesses are well-known risk factors of VTE. To avoid their potential confounding effects, we first limited the study to subjects without prior history of major noncardiovascular diseases and well-defined cardiovascular diseases that predict the occurrence of VTE (e.g. recent trauma). We then matched cases and controls on several covariates that may confound the association between the exposures and VTE. We also used multivariate conditional logistic regression in the analysis to adjust for other potential confounders, such as body mass index and hormone replacement therapy. The information on lipid-lowering drugs and/or other study drugs (e.g. aspirin) might have been incomplete because patients could have received these drugs at other hospitals/clinics, while the information was not noted in the medical record. The magnitude of such confounder misclassification, however, was unlikely to be substantial because most hyperlipidemic patients and patients who received the study drugs were frequent visitors to the study hospital. The information on remaining potential confounders was also likely to be rather complete and accurate, and the effects of residual confounding should be minimized.

In conclusion, we found a positive association between peripheral atherosclerotic disease and nondebilitating cerebrovascular disease and the risk of VTE. Although the finding on peripheral atherosclerotic disease should be interpreted with caution because the observed association was based on only 10 patients with the disease, we believe that our findings are valid. As a result, patients with these 2 diseases should receive more frequent evaluation for the risk of VTE and should even consider whether VTE prophylaxis is mandatory. Failure to identify and adequately control for the potential confounding effects of these diseases in any epidemiologic study would also result in an erroneous estimate of the effect of drug exposures on the risk of idiopathic VTE. The interpretation of any nonrandomized comparison of drug users and nonusers should therefore be cautious.

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