Diverticular Disease Is Associated With Increased Risk of Subsequent Arterial and Venous Thromboembolic Events

Lisa L. Strate,[*] Rune Erichsen,[‡] Erzsébet Horváth–Puhó,[‡] Lars Pedersen,[‡] John A. Baron,[§] and Henrik Toft Sørensen[‡]

[*]Department of Medicine, University of Washington School of Medicine, Seattle, Washington; [‡]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; and [§]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

BACKGROUND & AIMS: **Diverticular disease and cardiovascular disease share several risk factors. Inflammation associated with diverticular disease could predispose to cardiovascular disease. We assessed the association between a diagnosis of diverticular disease and subsequent arterial and venous thromboembolic events, adjusting for related comorbidities to explore a possible causal relationship.**

METHODS: **We identified 77,065 incident cases of diverticular disease from 1980–2011 from Danish nationwide medical registries; these were matched for age and sex with 302,572 population comparison cohort members. Individuals with a history of cardiovascular disease were excluded. We used Cox proportional hazards regression to compute incidence rate ratios, comparing the incidence of acute myocardial infarction, stroke, venous thromboembolism, and subarachnoid hemorrhage in patients with diverticular disease with those of the population cohort members, adjusting for age, sex, obesity, diabetes, hyperlipidemia, chronic obstructive pulmonary disease, connective tissue disease, renal disease, and treatments and medications.**

RESULTS: **The adjusted incidence rate ratios for patients with diverticular disease, compared with population cohort members, were 1.11 (95% confidence interval [CI], 1.07–1.14) for acute myocardial infarction, 1.11 (95% CI, 1.08–1.15) for overall stroke, 1.36 (95% CI, 1.30–1.43) for overall venous thromboembolism, and 1.27 (95% CI, 1.09–1.48) for subarachnoid hemorrhage. The relative risk of each event remained increased after we adjusted for changes in aspirin use or for endoscopy or colorectal surgery after the diagnosis of diverticular disease. These findings also held after excluding the first year of follow-up and limiting the analysis to patients with diverticulitis.**

CONCLUSIONS: **On the basis of an analysis of Danish medical registries, a diagnosis of diverticular disease is associated with a modest increase in risk of arterial and venous thromboembolic events after adjustment for related disorders.**

Keywords: Diverticulitis; Diverticular Bleeding; Inflammation; Comorbid Disease.

Diverticular disease and vascular disease, 2 sets of disorders that are prevalent in the developed world,[1,2] are generally thought to reflect different disease processes. However, there are several lines of evidence that suggest they may be associated. Diverticular disease and cardiovascular disease share a number of risk factors including obesity, physical inactivity, smoking, and low dietary fiber intake,[3] and these common risk factors alone could lead to an association. Modern theories propose that diverticulitis and perhaps diverticulosis occur in the setting of chronic intestinal inflammation that may lead to a low-grade inflammatory state.[4–6] Because chronic inflammation is implicated in the pathogenesis of cardiovascular disease, venous thromboembolism (VTE), and arterial atherosclerosis,[7–9] a causal link of diverticular disease with vascular disease is possible. In addition, diverticular disease, particularly diverticular bleeding and subarachnoid hemorrhage (SAH), may be linked to connective tissue defects and vascular rupture,[10,11] so a

Abbreviations used in this paper: **AMI, acute myocardial infarction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DNPR, Danish National Registry of Patients; DVT, deep venous thromboembolism; ICD, International Classification of Disease; IRR, incidence rate ratio; PE, pulmonary embolism; SAH, subarachnoid hemorrhage; SCAD, segmental colitis associated with diverticular disease; VTE, venous thromboembolism.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.11.026

similar association between diverticular disease and SAH might also be expected.

Several small case-control studies in Japan have found a significantly higher prevalence of hypertension and ischemic heart disease in patients with diverticular bleeding compared with controls.[12–15] A prospective male Swedish cohort identified hypertension as a risk factor for a hospital visit for diverticular disease.[16]

To our knowledge, no studies have examined the relationship between existing diverticular disease and subsequent cardiovascular and venous thromboembolic disease. Therefore, we examined the risk of acute myocardial infarction (AMI), stroke, VTE, and SAH in patients with a prior diagnosis of diverticular disease by using a prospective, population-based Danish cohort.

Methods

Study Population

We conducted a population-based cohort study[17] by using the Danish National Registry of Patients (DNPR)[18] and the Civil Registration System that encompass the entire Danish population.[19] The DNPR includes data on more than 99% of all discharges from non-psychiatric hospitals in Denmark since 1977. Emergency department and outpatient specialist clinic visits, including endoscopies, have been included since 1995. The DNPR contains data on admission and discharge dates, up to 20 discharge diagnoses (coded according to the International Classification of Diseases [ICD]), and procedures performed. A unique Civil Personal Registration number has been assigned to each resident since 1968, permitting longitudinal population follow-up and linkage across population registries. The Civil Registration System contains information on the date of death and emigration.

The study was approved by the Danish Protection Agency (record numbers 1-16-02-1-08 and 2011-41-5755) and was exempt from ethics committee review and participant consent because of use of registry data.

Diverticular Disease Cohort

We identified individuals in the DNPR with a first inpatient or outpatient primary or secondary diagnosis of diverticular disease during 1980–2011 on the basis of ICD codes (Supplementary Table 1). The positive predictive value of diagnostic coding for diverticular disease overall in the DNPR is 98%.[20] We excluded individuals with a history of cardiovascular disease including AMI, stroke, congestive heart failure, rheumatic heart disease, hypertension, and atrial fibrillation as well as VTE. We set 1980 as the study start date (instead of 1977 when the DNPR was established) to reduce the possibility of misclassification by left censoring of prevalent cardiovascular disease cases.

Population Comparison Cohort

We matched each diverticular disease patient on birth year and sex to 5 general population cohort members to form a population-based comparison cohort. Each comparison cohort member was alive on the date of diagnosis of the corresponding patient (the index date) and was free of prior cardiovascular disease (same exclusion criteria as for the diverticular disease cohort).

Arterial and Venous Vascular Disease

We used the DNRP to identify all inpatient and outpatient hospital contacts for AMI, ischemic and hemorrhagic stroke, SAH, VTE (deep venous thromboembolism [DVT] and pulmonary embolism [PE]) (Supplementary Table 1) among diverticular disease patients and members of the general population comparison cohort. The positive predictive values of ICD codes for AMI, stroke, SAH, and VTE in the DNPR are 94%, 90%, 79%, and 80%–90%, respectively.[21–23]

Other Risk Factors

We also used the DNRP to identify hospital diagnoses of a number of comorbid illnesses before and after the index date. These included obesity, diabetes, hyperlipidemia, chronic obstructive pulmonary disease (COPD), renal failure, and connective tissue disease (Supplementary Table 1). The ICD codes for COPD, connective tissue disorder, diabetes, and renal failure in the DNPR have positive predictive values of at least 95%.[24] In addition, we identified colon surgery or endoscopy occurring within 3 months after the index date (Supplementary Table 1). In a subanalysis, we used the Danish National Database of Reimbursed Prescriptions[25] to identify prescriptions for aspirin, statins, and calcium channel blockers. The Danish National Database of Reimbursed Prescriptions includes prescription data on reimbursed medications dispensed at Danish community and outpatient pharmacies since January 1, 2004. Partial reimbursement is available to all Danish citizens for prescribed medications.

Statistical Analysis

We followed subjects from their index date to the diagnosis of any arterial or venous thromboembolic event (AMI, stroke, VTE, or SAH), and we censored subjects at the time of emigration, the end of follow-up (December 31, 2011), or death. We used Cox proportional hazards regression to compute incidence rate ratios (IRRs) and 95% confidence intervals (CIs). We first computed unadjusted IRRs to assess the presence of any association. We then included age, sex, obesity, diabetes, hyperlipidemia, COPD, renal failure, and connective tissue disease as time-varying covariates in the models to