Thromboprophylaxis Is Associated With Reduced Post-hospitalization Venous Thromboembolic Events in Patients With Inflammatory Bowel Diseases

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BACKGROUND & AIMS: **Patients with inflammatory bowel diseases (IBDs) have increased risk for venous thromboembolism (VTE); those who require hospitalization have particularly high risk. Few hospitalized patients with IBD receive thromboprophylaxis. We analyzed the frequency of VTE after IBD-related hospitalization, risk factors for post-hospitalization VTE, and the efficacy of prophylaxis in preventing post-hospitalization VTE.**

METHODS: **In a retrospective study, we analyzed data from a multi-institutional cohort of patients with Crohn's disease or ulcerative colitis and at least 1 IBD-related hospitalization. Our primary outcome was a VTE event. All patients contributed person-time from the date of the index hospitalization to development of VTE, subsequent hospitalization, or end of follow-up. Our main predictor variable was pharmacologic thromboprophylaxis. Cox proportional hazard models adjusting for potential confounders were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).**

RESULTS: **From a cohort of 2788 patients with at least 1 IBD-related hospitalization, 62 patients developed VTE after discharge (2%). Incidences of VTE at 30, 60, 90, and 180 days after the index hospitalization were 3.7/1000, 4.1/1000, 5.4/1000, and 9.4/1000 person-days, respectively. Pharmacologic thromboprophylaxis during the index hospital stay was associated with a significantly lower risk of post-hospitalization VTE (HR, 0.46; 95% CI, 0.22–0.97). Increased numbers of comorbidities (HR, 1.30; 95% CI, 1.16–1.47) and need for corticosteroids before hospitalization (HR, 1.71; 95% CI, 1.02–2.87) were also independently associated with risk of VTE. Length of hospitalization or surgery during index hospitalization was not associated with post-hospitalization VTE.**

CONCLUSIONS: **Pharmacologic thromboprophylaxis during IBD-related hospitalization is associated with reduced risk of post-hospitalization VTE.**

Keywords: CD; UC; Clot; Vein; Vascular.

Patients with inflammatory bowel diseases (IBDs) (Crohn's disease [CD], ulcerative colitis [UC]) are at increased risk for venous thromboembolism (VTE)[1–7] and associated morbidity and mortality.[2,6] Inflammation is key determinant of VTE risk in IBD, with ambulatory flares and hospitalization being associated with increased risk.[1,2,5,6] Because the absolute VTE risk is greatest during hospitalization, experts recommend routine thromboprophylaxis in such settings.[6,8] However, despite the safety and efficacy of thromboprophylaxis, the rate of adoption remains low.[9,10]

In other settings at high risk for VTE such as after orthopedic surgery, the risk remains elevated for several

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9-CM, International Classification of Diseases, 9th Revision-Clinical Modification; IQR, interquartile range; OR, odds ratio; TNF, tumor necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolism.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.02.034

weeks because of persistence of risk factors such as limited mobility.[11] Conceivably, patients with IBD who have a severe disease flare requiring hospitalization remain at an elevated risk for VTE until inflammation resolves. Routine extended thromboprophylaxis is widely used after orthopedic surgery[11] but is not beneficial in general medical inpatients.[12] Prophylaxis during all ambulatory IBD flares may not be cost-effective,[13] but identification of subgroups of patients at a higher VTE risk may define those who could potentially experience greater benefit with extended thromboprophylaxis. Furthermore, the impact of thromboprophylaxis during hospitalization on subsequent risk of VTE has not been examined previously.

By using a large multi-institutional cohort of IBD patients, our aims were to (1) examine the frequency of VTE after an IBD-related hospitalization, (2) identify risk factors for post-hospitalization VTE events, and (3) define the use of thromboprophylaxis in an inpatient IBD population and examine its impact on subsequent risk of VTE.

Methods

Study Population

The data source for our study was an electronic medical record cohort of patients with CD and UC that has been described in our previous publications.[14–17] From a multihospital healthcare system in the Greater Boston area serving a population of more than 3 million patients, we identified all potential IBD patients by the presence of at least 1 International Classification of Diseases, 9th Revision-Clinical Modification (ICD-9-CM) code for CD (555.x) or UC (556.x). We extracted a range of codified data encompassing manifestations indicating severity or disease-related complications. From our electronic prescription system, we also extracted information on whether the patients had ever been prescribed medications used in the treatment of IBD including corticosteroids, mesalamine, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), or anti–tumor necrosis factor (TNF) biologic agents (infliximab, adalimumab, certolizumab pegol). We then extracted narrative free-text concepts identified by using natural language processing with the clinical Text Analysis and Knowledge Extraction System[18] as outlined in our previous publications. These could include terms such as "Crohn's disease," "ulcerative colitis," phrases used in endoscopic reports ("aphthous ulcers"), radiology ("ileal wall thickening"), or pathology reports ("ileitis"). We then developed an algorithm that used logistic regression with adaptive lasso to identify variables that predicted a diagnosis of CD or UC. This assigned each patient a probability between 0 and 1 of truly having CD or UC. We selected a cutoff for classifying disease that corresponded to a positive predictive value of 97%. The final algorithm was validated in an independent subset of patients and yielded our final IBD cohort of 5522 UC and 5506 CD patients when applied to the entire population of potential patients.

Cases of VTE were identified by the presence of validated ICD-9 codes for deep venous thrombosis, pulmonary embolism, intra-abdominal or portal thrombosis, and other thrombotic events such as cerebral thrombosis (ICD-9-CM 415.1, V125.1, 451.1–451.8, 453.0–453.9, 671.5, 325.0, 437.6, 671.9).[2,4,19,20] All VTE events were classified as occurring while inpatient or outpatient, and where this distinction was not possible, the events were labeled unclassified.

Variables

We extracted the patients' age including age at first diagnosis code for either CD or UC, gender, race (white or nonwhite), and defined comorbidity by using the validated Charlson comorbidity index.[21] We determined the occurrence of IBD-related hospitalizations or surgeries by using the primary reason for discharge among hospitalized patients. Medication use was defined as ever or never use before the event of interest. We also ascertained whether a patient had received a diagnosis of solid organ or metastatic tumor before the index hospitalization.

Primary Analysis: Predictors and Outcomes

Our primary analysis focused on occurrence of post-hospitalization VTE in adult IBD patients who had an IBD-related hospitalization or surgery. After excluding 22 patients who were on Coumadin at the time of the index hospitalization, we arrived at a final cohort of 2788 patients with CD or UC. Our main outcome variable was time to an outpatient VTE event. Patients who developed thrombosis during the initial hospitalization or during a subsequent hospitalization were excluded. Our main predictor of interest was receipt of venous thromboprophylaxis, namely the use of unfractionated heparin, enoxaparin, or dalteparin. We classified use of IBD-related medications as those occurring before the index hospitalization and extracted information on the duration of hospitalization and if it was related to a surgical procedure. In a subset of patients where this was available, we obtained information on the most recent laboratory markers of disease severity at the time of the index hospitalization including hemoglobin, albumin, serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, and white blood cell count.

Statistical Analysis

Analysis was performed by using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized by using medians and interquartile ranges (IQRs); categorical variables were expressed as