CLINICAL RESEARCH STUDY

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# Severity of Gastrointestinal Bleeding in Patients Treated with Direct-Acting Oral Anticoagulants

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## ABSTRACT

**BACKGROUND:** Direct-acting oral anticoagulants (DOACs), which have gained approval for stroke prevention in nonvalvular atrial fibrillation and treatment of venous thromboembolism, have become increasingly preferred over warfarin given their predictable pharmacodynamics, lack of required monitoring, and superior outcomes. Direct-acting oral anticoagulants have been shown to be associated with an increased frequency of gastrointestinal bleeding compared with warfarin, but the severity and characteristics of gastrointestinal bleeding in these patients is poorly understood.

**METHODS:** We retrospectively evaluated electronic medical records of patients with gastrointestinal bleeding (n = 8496) from 2010-2016. We identified 61 patients with gastrointestinal bleeding episodes while treated with DOACs (rivaroxaban, dabigatran, or apixaban) and 123 patients with gastrointestinal bleeding while taking warfarin. We randomly selected a control group of 296 patients with gastrointestinal bleeding who were not receiving anticoagulation treatment from the same sample. Outcomes included the need for hospitalization, blood transfusion, endoscopic or surgical intervention, and 30-day mortality.

**RESULTS:** The DOAC and warfarin groups were similar in terms of age and underlying comorbidity (assessed using the Charlson Comorbidity Index), but the DOAC group had greater concomitant aspirin use. Gastrointestinal bleeding was classified as upper (n = 186), lower (n = 88), anorectal (n = 183), small bowel (n = 9), and indeterminate (n = 14). After adjusting for differences in baseline variables, the DOAC group had fewer hospitalizations and required fewer transfusions than the warfarin group. The DOAC and control groups were not statistically different for all outcomes. There were no significant mortality differences among groups.

**CONCLUSION:** Although prior studies have shown a higher frequency of gastrointestinal bleeding in patients treated with DOACs compared with warfarin, our data suggest that gastrointestinal bleeding in patients taking DOACs may be less severe. These differences occurred despite significantly greater concomitant aspirin use in the DOAC group compared with warfarin users.

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**KEYWORDS:** Apixaban; Aspirin; Bleeding; Dabigatran; Direct-acting oral anticoagulant; Gastrointestinal; Hospitalization; Intervention; Mortality; Rivaroxaban; Severity; Transfusion; Warfarin

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**Authorship:** MMB: study concept and design; acquisition of data; review of clinical records; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. JCN: analysis and interpretation of data; choice of statistical methods; statistical analysis; formulation of tables and figures. TS: review of clinical records; analysis and interpretation of data; drafting of the manuscript. DCR: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; supervision of study conduct.

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The direct-acting oral anticoagulants (DOACs), which include the anti-factor Xa agents apixaban and rivaroxaban and the direct thrombin inhibitor dabigatran, have recently been approved for stroke prevention in nonvalvular atrial fibrillation as well as venous thromboembolism. These drugs are often preferred because of their predictable pharmacodynamics, lack of need for required monitoring, and superior outcomes.[1-3] Additionally, DOACs have a shorter time to peak effect (1-4 hours) compared with warfarin (4-5 days), shorter half-lives (5-17 hours vs 40 hours with warfarin), and fewer drug–drug interactions compared with warfarin.[4]

Although DOACs are associated with a significant decrease in the incidence of intracerebral hemorrhage and

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hemorrhagic stroke compared with patients treated with warfarin,[1-3,5,6] DOACs have been associated with an approximate 50% increase in the incidence of gastrointestinal bleeding compared with warfarin.[1-3,7] This has raised considerable concern about the absolute incidence of gastrointestinal bleeding associated with DOACs, because warfarin alone is associated with a 3-fold increase in risk of major gastrointestinal bleeding when compared with placebo, a risk increase that is doubled with the addition of antiplatelet agents.[7] Furthermore, costs are approximately 50% higher in patients who experience major gastrointestinal bleeding while being treated with warfarin compared with controls.[8]

Although it is accepted that the incidence of gastrointestinal bleeding in patients taking DOACs is increased, there are few data about the source and severity of gastrointestinal bleeding in patients treated with DOACs. Here, we hypothesized that DOACs not only may be associated with an increased incidence of gastrointestinal bleeding but also are associated with more severe gastrointestinal bleeding. Therefore, we examined the severity of gastrointestinal bleeding in patients treated with DOACs, warfarin, and no anticoagulation (control patients) as assessed by the need for hospitalization, blood transfusions, endoscopic or surgical intervention, and 30-day mortality.

**CLINICAL SIGNIFICANCE**

- Patients with gastrointestinal bleeding treated with direct-acting oral anticoagulants had less severe bleeding as assessed by the need for hospitalization and blood transfusion compared with patients treated with warfarin.
- Mortality rates were similar in patients treated with direct-acting oral anticoagulants, warfarin, and no anticoagulation.

## METHODS

### Study Population

We performed a retrospective case–control study of all adult patients (age ≥18 years) seen at the Medical University of South Carolina with gastrointestinal bleeding from January 1, 2010 to January 1, 2016. Patients were identified by an International Classification of Diseases, Ninth Revision Clinical Modification code search for gastrointestinal bleeding, which included the following: 569.3 (rectal and anal hemorrhage), 578.0 (hematemesis), 578.1 (blood in stool), and 578.9 (hemorrhage of gastrointestinal tract, unspecified). The electronic medical records of our study population were manually reviewed by 2 authors (MMB and TS) to confirm the diagnosis of gastrointestinal bleeding. If multiple encounters were identified, we analyzed the first encounter. We excluded patients with a clinical diagnosis of cirrhosis (owing to propensity for variceal bleeding), patients with severe thrombocytopenia (platelet count $<50 \times 10^3$), patients with hematologic disorders, and patients treated with clopidogrel or new antiplatelet agents.

Gastrointestinal bleeding was identified in 8496 patients (**Figure**). The resulting study sample included 61 patients with gastrointestinal bleeding while being treated with DOACs (apixaban, rivaroxaban, or dabigatran) and 123 patients treated with warfarin. We then randomly selected a control group of 296 patients with gastrointestinal bleeding not receiving anticoagulation (**Figure**). The study cohort thus included 480 unique patients with gastrointestinal bleeding in the outpatient setting, the emergency department, or admitted to the hospital.

The study was approved by the institutional review board at the Medical University of South Carolina.

### Data Collection and Definitions

We abstracted more than 60 unique variables for each patient at the time of presentation, including demographic, clinical, and historical data, such as the presence of previous gastrointestinal bleeding, medical comorbidities, indication for anticoagulation, concomitant aspirin use, endoscopic evaluation, source of bleeding, blood transfusions, hospital days, 30-day mortality, and complete laboratory data. Each subject's overall morbidity status was assessed using the Charlson Comorbidity Index (CCI), a formal scoring system including 22 medical comorbid conditions.[9] Clinical and laboratory variables reported were recorded at the time of presentation.

The diagnosis of gastrointestinal bleeding was made and confirmed by the documentation of witnessed hematemesis, melena, hematochezia, or any combination thereof by medical personnel accordging to the history and physical examination of the patient, with or without a positive fecal occult blood test results and with or without a significant drop in hemoglobin or hematocrit. Bleeding was characterized as upper, lower, anorectal, small bowel, or indeterminate on the basis of history and clinical presentation, history, and endoscopic findings. The finding of an endoscopic lesion documented to be consistent with bleeding in a specific location of the gastrointestinal tract assigned the source of bleeding to that portion of the gastrointestinal tract. With the exception of hematemesis, the source of bleeding was considered to be indeterminate if no endoscopy was performed. Indications for anticoagulation were determined according to review of history and clinical features.

Laboratory values included were those closest to the onset of bleeding. Laboratory values beyond 5 days from the onset of bleeding were excluded. Most patients who underwent endoscopy had the procedure performed acutely or early after the onset of gastrointestinal bleeding. Deferred endoscopic evaluation was included in this analysis only if the procedure occurred within 3 months and provided an explanation of the bleeding event.

Outcomes measured were need for hospitalization, number of hospital days, need for blood transfusion, number of trans-