Periprocedural Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant Undergoing a Digestive Endoscopy

Hansen-Barkun Christopher, BKin[1], Martel Myriam, MSc[1], Douketis James, MD[2], Neena S. Abraham, MD, MSc (Epi), MACG[3], Liederman Zachary, MD[4], Kaplovitch Eric, MD[5], Schulman Sam, MD, PhD[6,7], Alex C. Spyropoulos, MD[8,9], Majid Almadi, MD, MSc[10] and Alan N. Barkun, MD[11]

INTRODUCTION: **The periprocedural management of patients with atrial fibrillation (AF) using a direct oral anticoagulant (DOAC) undergoing elective gastrointestinal (GI) endoscopic procedure remains uncertain. We investigated the safety of a standardized periprocedural DOAC management strategy.**

METHODS: **The Periprocedural Anticoagulation Use for Surgery Evaluation cohort study enrolled adult patients receiving a DOAC (apixaban, rivaroxaban, or dabigatran) for AF scheduled for an elective procedure or surgery. This analysis addresses patients undergoing digestive endoscopy. Standardized periprocedural management consisted of DOAC interruption 1 day preendoscopy with resumption 1 day after procedure at low-moderate risk of bleeding or 2 days in case of a high bleeding risk. Thirty-day outcomes included GI bleeding, thromboembolic events, and mortality.**

RESULTS: **Of 556 patients on a DOAC (mean [SD] age of 72.5 [8.6] years; 37.4% female; mean $CHADS_2$ score 1.7 [1.0]), 8.6% were also on American Society of Anesthesiology (ASA) and 0.7% on clopidogrel. Most of the patients underwent colonoscopies (63.3%) or gastroscopies (14.0%), with 18.9% having both on the same procedural day. The mean total duration of DOAC interruption was 3.9 ± 1.6 days. Four patients experienced an arterial thromboembolic event (0.7%, 0.3%–1.8%) within 24.2 ± 5.9 days of DOAC interruption. GI bleeding events occurred in 2.5% (1.4%–4.2%) within 11.1 ± 8.1 days (range: 0.6; 25.5 days) of endoscopy, with major GI bleeding in 0.9% (0.4%–2.1%). Three patients died (0.5%; 0.2%–1.6%) 15.6–22.3 days after the endoscopy.**

DISCUSSION: **After a contemporary standardized periprocedural management strategy, patients with AF undergoing DOAC therapy interruption for elective digestive endoscopy experienced low rates of arterial thromboembolism and major bleeding.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C754

Am J Gastroenterol 2022;00:1–8. https://doi.org/10.14309/ajg.0000000000002076

INTRODUCTION

Patients on direct oral anticoagulants (DOAC) often require perioperative anticoagulant management around the time of an elective surgery/procedure, which is—often a gastrointestinal (GI) endoscopy (1). Perioperative DOAC interruption may increase the risk for thromboembolism, whereas continuation may increase the risk of postprocedural GI bleeding depending on the nature of the endoscopic procedure (2–4). Recent guidelines have proposed differing management strategies for patients on DOAC undergoing GI endoscopic procedures, partly because of limited and poor-certainty direct evidence (5–7).

The Periprocedural Anticoagulation Use for Surgery Evaluation (PAUSE) study was designed to assess the feasibility and safety of a standardized periprocedural and periprocedural

[1]Research Institute of the McGill University Health Center, Montreal, Quebec, Canada; [2]Department of Medicine, St. Joseph's Healthcare Hamilton and McMaster University, Hamilton, Ontario, Canada; [3]Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA; [4]University Health Network and Department of Medicine, The University of Toronto, Toronto, Ontario, Canada; [5]University Health Network and Sinai Health System, The University of Toronto, Toronto, Ontario, Canada; [6]Department of Medicine, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Ontario, Canada; [7]Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [8]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA; [9]Institute of Health System Science, The Feinstein Institutes for Medical Research, Manhasset, New York, USA; [10]Department of Medicine, King Saud University, Riyadh, Saudi Arabia; [11]Department of Medicine, McGill University and McGill University Health Center, Montreal, Quebec, Canada. **Correspondence:** Alan N. Barkun, MD. E-mail: alan.barkun@muhc.mcgill.ca.
Received March 23, 2022; accepted October 6, 2022; published online November 25, 2022

management strategy for a DOAC regimen (8). The main hypothesis was that a simple management approach, based on DOAC-specific interruption and resumption intervals while forgoing periprocedural heparin bridging and without the need for preoperative coagulation function testing, is feasible and safe. In an attempt to better inform current evidence-based recommendations, this study analyzes a large cohort of patients receiving a DOAC scheduled to undergo an elective GI endoscopic procedure, representing an important and more homogenous subgroup drawn from the larger published PAUSE cohort (8).

METHODS

The PAUSE study design and oversight

In the PAUSE cohort, safety was defined as excluding 30-day periprocedural rates of major bleeding of 2% and arterial thromboembolism of 1.5%, according to expected outcome rates (1% for major bleeding and 0.5% for arterial thromboembolism) observed with optimal periprocedural management of warfarin (1,9) and with a proof-of-concept prospective study of standardized periprocedural dabigatran management (10).

A dedicated steering committee developed the PAUSE study design and data analysis plan, described in detail elsewhere (11). The McMaster Center for Transfusion Research managed the study and was responsible for the study organization, data collection, validation, maintenance, and analysis. Study data were collected and managed using REDCap electronic data capture tools (12).

Patient population

Consecutive patients were included if adults (aged 18 years or older) with atrial fibrillation were long-term users of apixaban (5 mg or 2.5 mg twice daily), dabigatran etexilate (150 mg or 110 mg twice daily), or rivaroxaban (20 mg or 15 mg daily) and were able to adhere to the DOAC therapy interruption protocol during enrollment. They were excluded if 1 or more of the following were present: creatinine clearance (CrCl) $<$25 mL/min for apixaban users or CrCl $<$30 mL/min for dabigatran or rivaroxaban users, cognitive impairment or psychiatric illness, did not consent to participate, previous study participation, or more than 1 procedure planned within 30 days.

Intervention: The DOAC periprocedural interruption strategy. Patients were managed using a standardized periprocedural DOAC strategy based on DOAC pharmacokinetic properties (10- to 14-hour half-lives, and 1- to 3-hour peak action), the procedure-associated bleeding risk, and patient CrCl (11). Before the procedure, according to the original PAUSE protocol (11), DOAC regimens were omitted for 1 day before a low bleeding-risk procedure (36- to 42-hour interval corresponding to approximately 3 DOAC half-lives) and were omitted 2 days before a high bleeding-risk procedure (60- to 68-hour interval corresponding to approximately 5 DOAC half-lives); a longer interruption interval was required for patients using dabigatran with a CrCl $<$50 mL/min to account for renal dependence of dabigatran clearance (13). After the procedure, DOAC regimens were resumed 1 day (approximately 24 hours) after a low bleeding-risk procedure and 2–3 days (48–72 hours) after a high bleeding-risk procedure, provided hemostasis was achieved.

In the full PAUSE cohort, all elective digestive endoscopic procedures were initially considered low-risk bleeding-risk procedures (8). However, the PAUSE protocol allowed flexibility in the procedure-related bleeding risk classification and postprocedure management to account for real-life situations (11) in the opinion of the treating physicians.

Patient thromboembolic risk, based on the $CHADS_2$ risk score, did not affect periprocedural DOAC regimen management because this risk score is used in a periprocedural setting to assess the need for heparin bridging, which was not performed in this study (14,15). Patients at a high risk of venous thromboembolism were eligible for a prophylactic dose of heparin after the operation until DOAC therapy resumption.

All DOAC interruption time intervals were reported before or after the procedure's time until the resumption of the DOAC. Time estimates were rounded out to the nearest day for clinical pertinence and interpretability.

Outcomes

The primary clinical outcomes were major bleeding and arterial thromboembolism (ischemic stroke, transient ischemic attack, and systemic embolism). Secondary clinical outcomes included clinically relevant nonmajor bleeding, minor bleeding, death, myocardial infarction, deep vein thrombosis, pulmonary embolism, and catheter-associated venous or arterial thrombosis. All study outcomes were defined according to standardized criteria and were independently adjudicated by a committee that was blinded to the DOAC cohort, procedure bleeding risk, and preoperative DOAC treatment levels (that were also drawn as part of the PAUSE study) (8,16,17).

The criteria for categorizing major and minor bleeding were defined a priori and adapted from Douketis et al. (8). Study outcomes were assessed from when the first DOAC dose was interrupted until 30 days after the surgery/procedure. Patients had scheduled weekly telephone follow-up and additional clinic visits, as needed.

Statistical analysis

The unit of analysis is a patient for most of the results because the outcomes pertain to a given patient with each enrolled only once and some patients having 2 endoscopic procedures on the same day. Descriptive analyses were reported with categorical data expressed as proportions and 95% confidence interval and continuous data as mean values $\pm$ SD. Comparisons between groups were performed using the χ^2, Fisher exact, or t test, where appropriate. Ranges and medians were also used when appropriate. All statistical analyses were performed using SAS 9.4, SAS Institute, Cary, NC.

Ethics

The institutional review board of each of the 23 participating clinical centers in Canada, the United States, and Europe approved the PAUSE study protocol, and all study participants provided written informed consent.

RESULTS

Patient characteristics

Three thousand six hundred forty patients were screened between August 1, 2014, and July 31, 2018, at 23 clinical sites in Canada, the United States, and Europe, and 3,007 enrolled in the full PAUSE cohort (8). The subgroup of patients scheduled for an elective GI endoscopic procedure consisted of 579 participants. The procedure was canceled or rescheduled before DOAC interruption in 21 patients, with no follow-up information available in another 2.

Table 1. Demographics

	n/N (%) or mean ± std
Chronic nonvalvular or valvular AF	556/556 (100.0%)
Female	208/556 (37.4%)
Age	72.5 ± 8.6
Race	
African American	11/556 (2.0%)
Asian	7/556 (1.3%)
White	533/556 (95.9%)
East Indian	3/554 (0.5%)
Native Indian	2/556 (0.4%)
Previous stroke	62/554 (11.2%)
TIA	70/554 (12.6%)
Systemic embolism	2/556 (0.4%)
VTE	39/556 (7.0%)
Acute coronary syndrome	105/554 (19.0%)
Hypertension	424/556 (76.3%)
CHF	73/555 (13.2%)
Mitral valve disease	18/556 (3.2%)
Diabetes	171/556 (30.8%)
Cancer	129/554 (23.3%)
Antiplatelet therapy	56/556 (10.1%)
Aspirin	48/56 (85.7%)
Mean ASA dose (mg)	80.8 ± 0.4
80 mg	7/48 (14.6%)
81 mg	41/48 (85.4%)
Clopidogrel (Plavix)	4/56 (7.1%)
Cilostazol (Pletal)	0/56 (0.0%)
COX-2 NSAID (Celebrex)	2/56 (3.6%)
Dipyridamole (Aggrenox)	0/56 (0.0%)
NSAID (e.g., Advil)	4/56 (7.1%)
Pentoxifyline (Trental)	0/56 (0.0%)
Prasugrel (Effient)	0/56 (0.0%)
Ticagrelor (Brillinta)	0/56 (0.0%)
Ticlopidine (Ticlid)	0/56 (0.0%)
Other	0/56 (0.0%)
Continuing on ASA (if Aspirin = 1)	35/48 (72.9%)
Type of DOAC (dabigatran, rivaroxaban, and apixaban)	
Apixaban	216/556 (38.9%)
2.5 mg PO BID	29/216 (13.4%)
5 mg PO BID	187/216 (86.6%)
Mean dose (mg)	4.7 ± 0.9
Dabigatran	135/556 (24.3%)
110 mg PO BID	43/135 (31.9%)
150 mg PO BID	92/135 (68.2%)
Mean dose (mg)	137.3 ± 18.7
Rivaroxban	205/556 (36.9%)
15 mg PO OD	38/205 (18.5%)
20 mg PO OD	167/205 (81.5%)
Mean dose (mg)	19.1 ± 1.9
$CHADS_2$[a]	1.7 ± 1.0
Score 0	58/553 (10.5%)
Score 1–2	387/553 (70.0%)
Score 3–4	108/553 (19.5%)
CHA_2DS_2-VASc[b]	3.4 ± 1.5
HAS-BLED[c]	1.8 ± 0.7
Coronary stent	56/556 (10.1%)
Tissue heart valve	10/556 (1.8%)
Temporary interruption of NOAC for a prespecified elective surgery or invasive procedure	556/556 (100.0%)

AF, atrial fibrillation; BID, two times a day; CHF, congestive heart failure; DOAC, direct oral anticoagulant; NOAC, novel oral anticoagulants; NSAID, nonsteroidal anti-inflammatory drug; PO, per os; TIA, transient ischemic attack; VTE, venous thromboembolism.

[a]$CHADS_2$ risk score range: 1–6; risks include congestive heart failure, hypertension, age 75 yr or older, diabetes, and previous stroke or transient ischemic attack.

[b]$CHADS_2$–VA2Sc risk score range: 1–9; risks include congestive heart failure, hypertension, age 75 yr or older or 65 yr or older, diabetes, previous stroke or transient ischemic attack, female sex, and vascular disease.

[c]HAS-BLED, bleeding risk score range: 1–7; risks include hypertension, abnormal renal or liver function, previous stroke, previous bleed or bleed predisposition, labile international normalized ratio (omitted), age 65 yr or older, and drug use that affects hemostasis or alcohol use (omitted).

The study cohort included 208 female participants (37.4%), with a mean age of 72.5 ± 8.6 years (Table 1). Overall, 11.2% of patients had a history of stroke, 12.6% had a transient ischemic attack, 0.4% had a systemic embolism, and 7.0% had previous venous thromboembolism; 38.9% were on apixaban, 24.3% on dabigatran, and 36.9% on rivaroxaban, while 10.1% of patients also received antiplatelet therapy. Of these patients, American Society of Anesthesiology (ASA) was the most prescribed (85.7%), followed by clopidogrel (7.1%) or other nonsteroidal anti-inflammatory drug (7.1%). Dual antiplatelet therapy (ASA and clopidogrel) was used in 4.1% of patients. The mean $CHADS_2$ score was 1.7 ± 1.0, and the mean CHA_2DS_2-VASc and HAS-BLED were 3.4 ± 1.5 and 1.8 ± 0.7, respectively.

DOAC interruption. Most of the patients (525, 94.4%) were classified as undergoing a low/moderate bleed-risk GI, in keeping with the assigned PAUSE classification of routine GI endoscopies (8).

One patient underwent a 2-day preprocedural interruption due to chronic kidney disease (CrCl <50 mL/min) while on dabigatran, as required by the PAUSE protocol. Reasons for preprocedural protocol deviation that occurred in 56 patients are listed in Appendix (see Supplementary Digital Content, http://links.lww.com/AJG/C754).

Table 2. DOAC interruption duration preprocedure and postprocedure

Variable	n/N (%) or mean ± std
No. of days skipped preprocedure[a]	
Mean	2.0 ± 0.5
1–2	495/551 (89.8%)
3 or more	56/551 (10.2%)
No. of days postprocedure	
Mean	1.9 ± 1.5
1	306/547 (55.9%)
2	94/547 (17.2%)
3 or more	147/547 (26.9%)

DOAC, direct oral anticoagulant.
[a]This interval of time at which the DOAC is stopped corresponds to instructions for stopping it 1 day before the procedure; the actual preprocedural interruption time overall exceeds 1 day because of variations as to when patients ingested the last DOAC, dose, and/or when they underwent the endoscopy on the day of the procedure.

The DOAC was restarted 1 day after the procedure in 55.9%, 2 days after the procedure in 17.2%, and 3 days or more (range: 0–7 days) in 26.9% of patients. DOAC interruption times preprocedure and postprocedure are detailed in Table 2.

The mean total duration of DOAC interruption was 3.9 ± 1.6 days and included 2.0 ± 0.5 days up to the exact time of the procedure and 1.9 ± 1.5 days postprocedure, including the postendoscopy time elapsed on the day of the procedure. There were 0.4% (2/550) of patients deemed at a high risk for venous thromboembolism who received prophylactic dose of heparin after the endoscopy until DOAC therapy resumption.

On the day of the procedure, 8.9% of all patients received antiplatelet therapy, of whom 85.7% were taking ASA and 6.1% each on clopidogrel or an nonsteroidal anti-inflammatory drug.

Primary and secondary outcomes

Thromboembolic events were reported in 4 patients (0.7% [0.3%–1.8%]) 24.2 ± 5.9 days from the date of DOAC procedural interruption (range: 2.0–29.6 days). These included a patient with a myocardial infarction 2 days after stopping dabigatran and further complicated by a stroke and an acute ST segment elevation myocardial infarction. Another patient experienced an acute coronary syndrome 11 days after restarting rivaroxaban. Two other patients developed a transient ischemic attack 22 and 24 days after restarting apixaban. Only 1 of the 4 events was adjudicated as related to the periprocedural DOAC interruption (0.18% [0.03%–1.01%]).

A bleeding event of any type (endoscopy-related or other) occurred in 24 (4.4%) patients, on average 10.3 ± 7.7 days (range 0.6–25.5 days) after the procedure. Postendoscopy GI bleeding occurred in 14 patients (2.5% [1.4%–4.2%] 11.1 ± 8.1 days [range: 0.6–25.5 days]) after the endoscopy (Table 3) and 8.0 ± 6.8 days (range: 0–24 days) after DOAC resumption (Figure 1). The bleeding event preceded DOAC resumption in 1 patient. Among the 14 GI bleeding events, 5 (35.7%) were classified as major for an overall rate of major GI bleeding of 0.9% (0.4%–2.1%).

Table 3. Outcomes

Variable	n/N (%) % (95% CI) or mean ± std
Thromboembolic event	4/552 (0.7%) 0.7% (0.3%–1.8%)
Procedure to thromboembolic event (d)	21.9 ± 6.0
Last dose DOAC to thromboembolic event (d)	24.2 ± 5.9
All bleeding event	24/552 (4.4%)
GI bleeding	14/552 (2.5%; 1.4%–4.2%)
Major GI bleeding[a]	5/552 (0.9%; 0.4%–2.1%)
Time from procedure to date of bleed	11.1 ± 8.1
Procedure	
Colonoscopy only	9/11 (81.8%)
Flexible sigmoidoscopy only	0/11 (0.0%)
Gastroscopy only	1/11 (9.1%)
Colonoscopy and gastroscopy	1/11 (9.1%)
New admission due to GI bleeding	7/14 (50.0%)
Mortality	3/552 (0.5%) 0.5 (0.2; 1.6)
Time procedure to death	19.0 ± 4.7

CI, confidence interval; DOAC, direct oral anticoagulant; GI, gastrointestinal.
[a]Major bleeding is defined as fatal bleeding; bleeding causing a drop in hemoglobin 20 g/L (1.24 mmol/L); bleeding leading to transfusion of 2 units of whole blood or red cells within 48 hours of the bleed; bleeding that leads to intervention; bleeding requiring intervention resulting in prolonged care or stay; bleeding that is unexpected or prolonged; bleeding sufficiently large to cause hemodynamic instability associated with drop in hemoglobin 20 g/L (1.24 mmol/L) within 48 hours of seeking medical help; bleeding sufficiently large to cause hemodynamic instability associated with transfusion of 2 units of whole blood or red cells within 48 hours of the bleed.
Outcomes were missing for 4 patients who had the procedure (length of stay).

Three patients died (0.5%; 0.2%–1.6%) after a mean of 19.0 ± 4.7 days (range 15.6–22.3 days) from the time of the procedure. Two deaths occurred after developing a thromboembolic event. A third patient died because of complications following an esophagectomy 6 days after a gastroscopy without apixaban resumption. Seven (50%) of all patients experiencing GI bleed required admission to the hospital, including patients experiencing clinically relevant nonmajor bleeding, as defined *a priori* (11) (Table 3).

DOAC interruption and bleeding outcomes according to the nature of the digestive endoscopy. More detailed procedural information was available in 466 patients undergoing 554 endoscopic procedures. These included a colonoscopy (63.3%), a gastroscopy (14.0%), a sigmoidoscopy (3.7%), or an ileoscopy (0.2%) alone, while both a gastroscopy and a colonoscopy were performed on the same procedural day in another 88 (18.9%) patients (Table 2). Population characteristics were similar in the 90 patients for whom detailed procedural information was unavailable (data available on request).

Based on the preprocedural assessment as to the nature of the endoscopic procedure, 408 (87.6%) patients underwent a gastroscopy or ileoscopy with planned therapy, a colonoscopy,

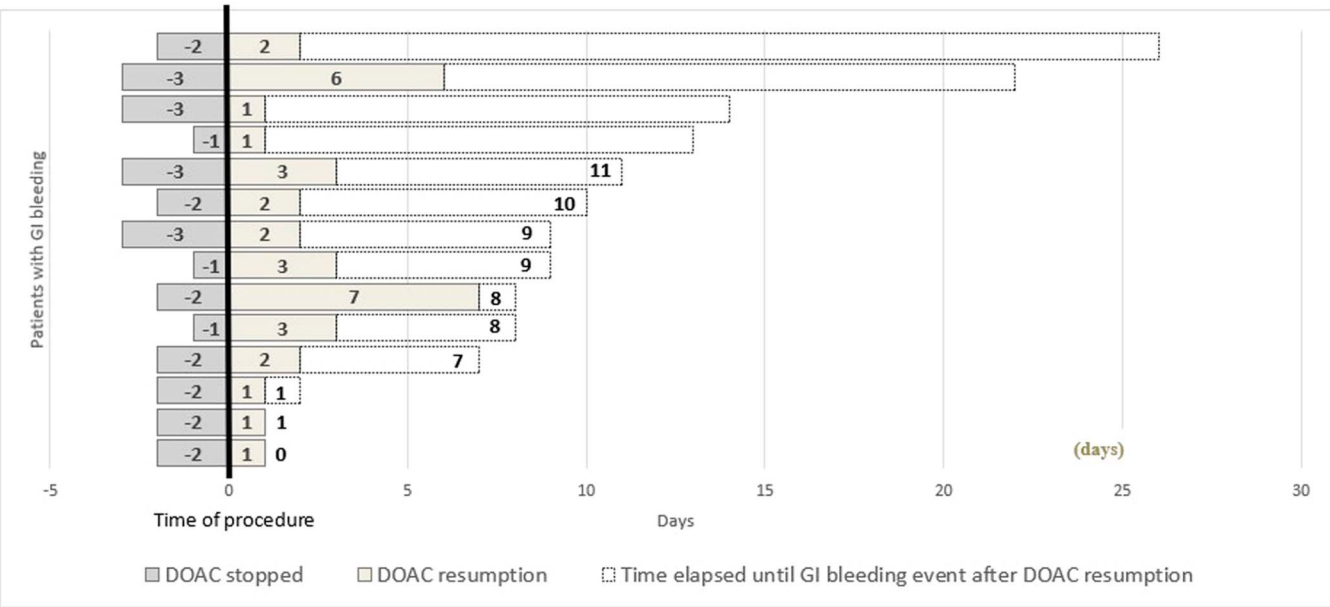

Figure 1. Timing of GI bleeding event for DOAC management and GI endoscopic procedure in days. DOAC, direct oral anticoagulant; GI, gastrointestinal.

sigmoidoscopy, or ileoscopy in which the DOAC was stopped 2.0 ± 0.5 days (range: 0–4 days) before the endoscopic procedure. Of the 58 (12.5%) patients in whom only a regular gastroscopy (±biopsies) was planned, the DOAC was stopped 2.0 ± 0.8 days (range: 1–7 days) before the procedure.

Among the 27 patients in whom the available intraprocedural information confirmed a high risk of rebleeding as per American Society for Gastrointestinal Endoscopy criteria (78% of whom had undergone a colonic polypectomy), the DOAC was restarted in 41%, 18%, and 41% of patients 1, 2, or 3 or more days after the endoscopy, respectively.

Among the 14 patients who experienced postprocedural GI bleeding, 9 had undergone a colonoscopy alone, 1 had undergone a gastroscopy alone, and 1 had undergone both procedures on the same day (no additional intraprocedural information in these, and the type of endoscopy unspecified in 3). Detailed information was available on the 14 patients who experienced postprocedural GI bleeding. Of them, 5 had major bleeding episodes with 4 receiving blood transfusions and 2 requiring repeat colonoscopy and endoscopic clip hemostasis at a postpolypectomy site; another patient underwent an ileoscopy that failed to show a site of bleeding. Two patients had a computed tomography scan and one a computed tomography enterography. The other 9 patients did not require hospitalization, blood transfusions, or a repeat endoscopy. Figure 1 displays the timing of GI bleeding event for DOAC management and GI endoscopic procedure.

DISCUSSION

Our study found a low rate of arterial thromboembolism (0.7%) and GI bleeding (2.5%) using the standardized protocol of periprocedural DOAC interruption and resumption based on procedural bleed risk and DOAC pharmacokinetic properties in a large group of consecutive patients undergoing elective GI procedures as part of the PAUSE study. Notwithstanding poorly characterized patient and physician preferences (18), contemporary periendoscopic DOAC management remains disparate with significant discrepancies in existing GI guidelines (5–7,19) and resulting poor adherence rates to these (20). Indeed, such recommendations have had to contend with evolving evidence such as recent data refuting the need for heparin bridging to avoid thrombosis for both patients on vitamin K antagonists or a DOAC (and may in fact cause increased bleeding) (11,21,22) and changing endoscopic approaches aimed at further decreasing postprocedural bleeding (23). Guideline panels have also had to contend with a lack of high-quality data addressing DOAC interruption. Methodological limitations have included retrospective data collection, small sample size, incomplete results or lack of appropriate controls precluding precise risk estimates, varying definitions of outcomes, the inclusion of elective and urgent procedures of all types with markedly disparate risks of post-endoscopy bleeding, and the inclusion of heparin bridging, which confounds bleeding outcomes. Perhaps most importantly, no prospective study has adopted an *a priori* standardized DOAC interruption regimen.

The PAUSE study addresses many of these shortcomings and is the only prospective clinical study that assessed a standardized periprocedural DOAC management strategy that involved a large group of consecutive patients undergoing GI endoscopy while adopting *a priori* definitions of outcomes that blinded assessors subsequently adjudicated. The PAUSE protocol is based on contemporary pharmacodynamic principles and aims for the shortest safe DOAC interruption, minimizing risks of thromboembolism while reducing postprocedural bleeding (11). The DOAC interruption protocol was also designed to be easily understood by patients and broadly adopted by clinicians, allowing for individualized management according to perceived procedural risk. The full PAUSE cohort assessed a wide sampling of operations/procedures, with the current analysis focusing specifically on digestive endoscopies. The original sample size calculation of the PAUSE cohort study (n = 3,007) aimed to be adequately powered to detect incidence rates of 1% for both thromboembolic and bleeding events. This subgroup analysis with n = 566 patients (and 99.6% 30-day follow-up data) results of course in broader confidence intervals that were 0.7% (0.3%–1.8%) for thromboembolic events and 2.5% (1.4%–4.2%) for GI bleeding events.

Patient population characteristics demonstrate a broadly generalizable risk profile for antithrombotic risk (n = 556, mean age of 72.5 years, mean $CHADS_2$ score = 1.7), with 10.1% of patients receiving antiplatelet therapy in addition to a DOAC. Despite some missing detailed intraprocedural information, the nature, number, and breadth of what are commonly performed GI endoscopies provide important and representative outcome estimates of thromboembolic and postendoscopy bleeding rates that can be encountered in a general GI practice.

Most patients were allocated to the briefest DOAC interruption intervals both preprocedureand postprocedure provided by the PAUSE management protocol, (1 day before and 1 day after the GI endoscopy in addition to the day of the procedure), resulting in a mean total duration of DOAC interruption of 3.9 days. This duration included 2.0 days up to the exact time of the procedure and 1.9 days postprocedure, including the postendoscopy time elapsed on the day of the procedure. This study was one of the key references identified in the American College of Gastroenterologists guidelines on the management of antithrombotics before a scheduled GI endoscopy (24). In fact, this subgroup analysis was completed specifically with the aim of informing the ACG guidelines. The pertinent conclusions state that from the limited available data, the panel suggests temporary interruption of the DOAC that is preferred over continued DOAC administration. The discussion pertaining to that recommendation states that the duration of temporary DOAC interruption before endoscopic procedures associated with favorable outcomes is between 1 and 2 days, excluding the day of the procedure, which permits the shortest preprocedural duration of DOAC interruption while balancing bleeding and thromboembolism risk.

This conclusion stems specifically from the PAUSE cohort for patients undergoing a digestive endoscopy, which have represented principally diagnostic procedures with or without biopsies, although the lack of granularity of endoscopic information limits this assumption with unclear extension to therapeutic procedures known to be such *a priori*. It is important to mention that past guidelines differ from the PAUSE protocol in that they recommend shorter preprocedure interruption for sole diagnostic procedures, including colonoscopies (5,7). Whether shorter durations of preprocedural interruption could further decrease thrombotic complications remains unstudied. Moreover, a limitation of such recommendations is the lack of being able to predict which patient will require a polypectomy at colonoscopy in most cases.

Despite including all patients independent of thromboembolic risk except for those with more advanced renal failure, thromboembolic events were reported in only 4 patients (0.7%), on average 24.2 days from the date of DOAC procedural interruption (range: 2.0–29.6 days). Of importance, only 1 of the 4 events was adjudicated as related to the periprocedural DOAC interruption (0.18%), with the other 3 events occurring 11–24 days after DOAC resumption. Reported thromboembolic risks in anticoagulated patients undergoing elective endoscopy reached 5.4% in a nationwide Japanese cohort (25), although lower 30-day thromboembolic rates more in keeping with our findings were reported in an Italian cohort of 529 patients (0.4%) (26) and a Spanish cohort of 598 patients (0.7%) (27).

A GI bleeding event occurred in 14 patients (2.5%) within 11.1 days (range: 0.6–25.5 days) of the endoscopy, with major GI bleeding in 0.9% and 50.0% requiring hospital admission. A per procedural analysis of the results is limited due to unavailable intraprocedural information. However, among 11 of the 14 patients who experienced postprocedural GI bleeding, 9 had undergone a colonoscopy only, 1 a gastroscopy only, and another had undergone both procedures on the same day. Figure 1 displays the relationship between the timing of the bleeding event and postendoscopic DOAC resumption, demonstrating a similar bimodal distribution of bleeding events as in patients not taking anticoagulants (28). The incidence of bleeding events, although similar to some reports (29), most of whom addressed postpolypectomy bleeding (30,31), was lower than that reported in most large cohorts of patients on DOAC undergoing a wide range of endoscopic procedures (6.7%–9.9%). This discrepancy may be because of the performance of higher-risk procedures and the use of heparin bridging in the latter (25,26,32,33). Indeed, the endoscopies performed in the PAUSE cohort included a large proportion of gastroscopies and colonoscopies with what were likely diagnostic procedures with or without biopsies and the removal of small colonic polyps. These are procedures that are associated with a low risk of bleeding, even in anticoagulated patient population (26,27,34–36), in contrast to higher-risk endoscopies such as endoscopic retrograde cholangiopancreatography and endoscopic submucosal dissection (22,25,26,32,33,37,38). Again, the lack of detailed intraprocedural information and scarcity of patients undergoing more sophisticated advanced endoscopic procedures does not allow our PAUSE subanalysis data to further inform guidelines on this aspect of management. Of interest, delayed anticoagulant resumption does not seem to reduce the risk of postprocedural bleeding (32,39), perhaps partly because of the delayed timing of such bleeding. A recent observational study from Japan suggested that cold snare polypectomy for polyps $\leq$10 mm may be safely performed if direct-acting oral anticoagulants are withheld only on the day of the procedure (38,40). Recent reports suggesting limited added benefits when combining dual antiplatelet therapy to an oral anticoagulant in some high-risk patients (as was the case for some participants in our cohort) may lead to a change in prescribing that could further decrease periprocedural bleeding (41). Regarding any possible interpretation of between-molecule significance in delayed bleeding, such comparison has yielded varied conclusions in the literature and is limited, as is the case in this study, by small numbers of events.

The very low arterial thromboembolic risk of adjudicated thromboembolic events and few clinically significant postprocedural bleeding events associated with the PAUSE protocol for standardized temporary interruption and resumption of DOAC suggests its adoption for most endoscopic procedures, although some uncertainty persists concerning colonoscopy with polypectomy. An insufficient number and diversity of advanced endoscopic procedures limits the ability to verify the safety of the PAUSE protocol in this clinical setting; additional studies are required to assess the optimal postprocedural DOAC resumption regimen.

CONFLICTS OF INTEREST

Guarantor of the article: Alan N. Barkun, MD.

Specific author contributions: H.-B.C., M.M., D.J., N.S.A., L.Z., K.E., S.S., A.C.S., M.A., A.N.B.: study concept and design. D.J., L.Z., K.E.: acquisition of data. H.-B.C., M.M., D.J., N.S.A., L.Z., K.E., S.S., A.C.S., M.A., A.N.B.: analysis and interpretation of data. H.-B.C., M.M., D.J., N.S.A., L.Z., K.E., M.A., A.N.B.: drafting of the manuscript. H.-B.C., M.M., D.J., N.S.A., L.Z., K.E., S.S., A.C.S., M.A.,

A.N.B.: critical revision of the manuscript for important intellectual content. H.-B.C., M.M., A.N.B.: statistical analysis. M.A.: obtained funding. A.N.B.: study supervision.

Financial support: The authors extend their appreciation to the International Scientific Partnership Program ISPP at King Saud University for funding this research work through ISPP-21-156(1).

Potential competing interests: H.-B.C. has no conflict of interest; M.M. has no conflict of interest; D.J. has reported personal fees from The Merck Manual and up to date; consulting fees from Bayer, Jenssen, Leo Pharma, Servier, and Bristol-Myers Squibb; speaker fees from Pfizer, Leo Pharma, and Sanofi. N.S.A. and L.Z. have no conflict of interest; K.E. has no conflict of interest; Sam Schulman research funding from Boehringer Ingelheim and Octapharma and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi. A.C.S.: consult with Janssen, Bayer, Boehringer Ingelheim, and BMS. M.A. has no conflict of interest; A.N.B.: consulting for Pendopharm and Astrazeneca Canada Olympus Cook; research support from Imagia.

Study Highlights

WHAT IS KNOWN

- ✓ A significant proportion of patients undergoing an elective digestive endoscopy is on a direct oral anticoagulant (DOAC).
- ✓ The optimal approach to temporary DOAC interruption in this setting remains poorly characterized.
- ✓ Societal recommendations are discrepant with outdated guidance in many cases.

WHAT IS NEW HERE

- ✓ The Periprocedural Anticoagulation Use for Surgery Evaluation (PAUSE) DOAC interruption management strategy is an approach based on sound pharmacokinetic principles adapted to a simple stratified categorization of anticipated periprocedural bleeding risks.
- ✓ The PAUSE cohort subgroup presented is the first true prospective study assessing a representative group of patients at varying risks of thrombosis on a DOAC who are scheduled to undergo common endoscopic procedures. These patients were assigned to a standardized management scheme with defined outcomes and full 30-day follow-up.
- ✓ The very low thromboembolic risk of adjudicated thromboembolic events (0.7%) and few major postprocedural bleeding events (0.9%) associated with the PAUSE protocol support its use for most endoscopic procedures, including colonoscopy with polypectomy.
- ✓ Additional studies are required to better determine the optimal postprocedural DOAC resumption regimen and particularly in patients with colonoscopy due to the limited procedural information available in the PAUSE cohort.

REFERENCES

1. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: Results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. Circulation 2012;126:343–8.
2. Abraham NS, Noseworthy PA, Inselman J, et al. Risk of gastrointestinal bleeding increases with combinations of antithrombotic agents and patient Age. Clin Gastroenterol Hepatol 2020;18:337–46.e19.
3. Abraham NS, Noseworthy PA, Yao X, et al. Gastrointestinal safety of direct oral anticoagulants: A large population-based study. Gastroenterology 2017;152:1014–22.e1.
4. Rodríguez de Santiago E, Sánchez Aldehuelo R, Riu Pons F, et al. Endoscopy-related bleeding and thromboembolic events in patients on direct oral anticoagulants or vitamin K antagonists. Clin Gastroenterol Hepatol 2021;20:e380–97.
5. Acosta RD, Abraham NS, Chandrasekhara V, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83:3–16.
6. Chan FKL, Goh KL, Reddy N, et al. Management of patients on antithrombotic agents undergoing emergency and elective endoscopy: Joint asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) Practice guidelines. Gut 2018;67:405–17.
7. Veitch AM, Radaelli F, Alikhan R, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. Gut 2021;70:1611–28.
8. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med 2019;179:1469–78.
9. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: Systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012;126: 1630–9.
10. Schulman S, Carrier M, Lee AY, et al. Perioperative management of dabigatran: A prospective cohort study. Circulation 2015;132:167–73.
11. Douketis JD, Spyropoulos AC, Anderson JM, et al. The perioperative anticoagulant use for surgery evaluation (PAUSE) study for patients on a direct oral anticoagulant who need an elective surgery or procedure: Design and rationale. Thromb Haemost 2017;117:2415–24.
12. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. Epidemiology 2007;18:805–35.
13. Spyropoulos AC, Al-Badri A, Sherwood MW, et al. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. J Thromb Haemost 2016;14:875–85.
14. Doherty JU, Gluckman TJ, Hucker WJ, et al. ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: A report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69:871–98.
15. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice guidelines. Chest 2012;141:e326S–50S.
16. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202–4.
17. Spyropoulos AC, Douketis JD, Gerotziafas G, et al. Periprocedural antithrombotic and bridging therapy: Recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. J Thromb Haemost 2012;10:692–4.
18. Taghiakbari M, Pohl H, Djinbachian R, et al. What size cutoff level should be used to implement optical polyp diagnosis? Endoscopy 2022. doi: 10.1055/a-1843-9535. Online ahead of print.
19. Chapelle N, Martel M, Bardou M, et al. Role of the endoscopic Doppler probe in nonvariceal upper gastrointestinal bleeding: Systematic review and meta-analysis. Dig Endosc 2022. doi: 10.1111/den.14356. Online ahead of print.
20. Jiang W, Suen BY, Ho HT, et al. Impact of physicians' and patients' compliance on outcomes of colonoscopic polypectomy with anti-thrombotic therapy. Clin Gastroenterol Hepatol 2021;19:2559–66.e1.
21. Douketis JD, Hasselblad V, Ortel TL. Bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2016;374:93–4.
22. Barkun AN, Laine L, Leontiadis GI, et al. Over-the-scope clips versus standard treatment. Gut 2022; gutjnl-2022-327712. doi: 10.1136/gutjnl-2022-327712. Online ahead of print.
23. Spadaccini M, Albeniz E, Pohl H, et al. Prophylactic clipping after colorectal endoscopic resection prevents bleeding of large, proximal polyps: Meta-analysis of randomized trials. Gastroenterology 2020;159: 148–58.e11.

24. Abraham NS, Barkun AN, Sauer BG, et al. American College of Gastroenterology-Canadian Association of Gastroenterology Clinical Practice guideline: Management of anticoagulants and antiplatelets during acute gastrointestinal bleeding and the periendoscopic period. Am J Gastroenterol 2022;117:542–58.
25. Nagata N, Yasunaga H, Matsui H, et al. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: Results from a large nationwide database analysis. Gut 2018;67:1805–12.
26. Radaelli F, Fuccio L, Paggi S, et al. Periendoscopic management of direct oral anticoagulants: A prospective cohort study. Gut 2019;68:969–76.
27. Rodriguez de Santiago E, Sanchez Aldehuelo R, Riu Pons F, et al. Endoscopy-related bleeding and thromboembolic events in patients on direct oral anticoagulants or vitamin K antagonists. Clin Gastroenterol Hepatol 2022;20:e380–97.
28. Rabeneck L, Saskin R, Paszat LF. Onset and clinical course of bleeding and perforation after outpatient colonoscopy: A population-based study. Gastrointest Endosc 2011;73:520–3.
29. Heublein V, Pannach S, Daschkow K, et al. Gastrointestinal endoscopy in patients receiving novel direct oral anticoagulants: Results from the prospective Dresden NOAC registry. J Gastroenterol 2018;53:236–46.
30. Yan Z, Gao F, Xie J, et al. Incidence and risk factors of colorectal delayed post-polypectomy bleeding in patients taking antithrombotics. J Dig Dis 2021;22:481–7.
31. Kim GU, Lee S, Choe J, et al. Risk of postpolypectomy bleeding in patients taking direct oral anticoagulants or clopidogrel. Sci Rep 2021;11:2634.
32. Rodriguez de Santiago E, Hernandez-Tejero M, Rivero-Sanchez L, et al. Management and outcomes of bleeding within 30 Days of colonic polypectomy in a large, real-life, multicenter cohort study. Clin Gastroenterol Hepatol 2021;19:732–42.e6.
33. Harada H, Miyaoka Y, Yuki T, et al. Postpolypectomy bleeding of colorectal polyps in patients with continuous warfarin and short-term interruption of direct oral anticoagulants. Gastrointest Endosc 2021;93:691–8.
34. Ara N, Iijima K, Maejima R, et al. Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. Dig Endosc 2015;27:458–64.
35. Tompkins EL, Andrews MA, Nojima M. Continuous anticoagulation and cold snare polypectomy. Ann Intern Med 2019;171:863–4.
36. Yabe K, Horiuchi A, Kudo T, et al. Risk of gastrointestinal endoscopic procedure-related bleeding in patients with or without continued antithrombotic therapy. Dig Dis Sci 2021;66:1548–55.
37. Tomida H, Yoshio T, Igarashi K, et al. Influence of anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection: A multicenter retrospective study. Gastric Cancer 2021;24:179–89.
38. Kubo K, Kato M, Mabe K, et al. Risk factors for delayed bleeding after therapeutic gastrointestinal endoscopy in patients receiving oral anticoagulants: A multicenter retrospective study. Digestion 2021;102:161–9.
39. Chebaa BR, Burgman B, Smith AD, et al. Timing of resumption of anticoagulation after polypectomy and frequency of post-procedural complications: A post-hoc analysis. Dig Dis Sci 2022;67:3210–9.
40. Morita A, Horiuchi I, Tanaka N, et al. Managing bleeding risk after cold snare polypectomy in patients receiving direct-acting oral anticoagulants. Gastrointest Endosc 2022;95:969–74.
41. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J 2019;40:3757–67.