ORIGINAL ARTICLE

Periendoscopic management of direct oral anticoagulants: a prospective cohort study

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ABSTRACT

Objective To assess the frequency of adverse events associated with periendoscopic management of direct oral anticoagulants (DOACs) in patients undergoing elective GI endoscopy and the efficacy and safety of the British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) recommendations (NCT 02734316).

Design Consecutive patients on DOACs scheduled for elective GI endoscopy were prospectively included. The timing of DOAC interruption and resumption before and after the procedures were recorded, along with clinical and procedural data. Procedures were stratified into low-risk and high-risk for GI-related bleeding, and patients into low-risk and high-risk for thromboembolic events. Patients were followed-up for 30 days for major and clinically relevant non-major bleeding events (CRNMB), arterial and venous thromboembolism and death.

Results Of 529 patients, 38% and 62% underwent high-risk and low-risk procedures, respectively. There were 45 (8.5%; 95% CI 6.3% to 11.2%) major or CRNMB events and 2 (0.4%; 95% CI 0% to 1.4%) thromboembolic events (transient ischaemic attacks). Overall, the incidence of bleeding events was 1.8% (95% CI 0.7% to 4%) and 19.3% (95% CI 14.1% to 25.4%) in low-risk and high-risk procedures, respectively. For high-risk procedures, the incidence of intraprocedural bleeding was similar in patients who interrupted anticoagulation according to BSG/ESGE guidelines or earlier (10.3%vs10.8%, p=0.99), with a trend for a lower risk as compared with those who stopped anticoagulation later (10.3%vs25%, p=0.07). The incidence of delayed bleeding appeared similar in patients who resumed anticoagulation according to BSG/ESGE guidelines or later (6.6%vs7.7%, p=0.76), but it tended to increase when DOAC was resumed earlier (14.4%vs6.6%, p=0.27). The risk of delayed major bleeding was significantly higher in patients receiving heparin bridging than in non-bridged ones (26.6%vs5.9%, p=0.017).

Conclusion High-risk procedures in patients on DOACs are associated with a substantial risk of bleeding, further increased by heparin bridging. Adoption of the BSG/ESGE guidelines in periendoscopic management of DOACs seems to result in a favourable benefit/risk ratio.

Trial registration number NCT 02734316; Pre-results.

Significance of this study

What is already known on this subject?

- Management of direct oral anticoagulants (DOACs) in patients undergoing GI endoscopy has become a common clinical challenge for which best practice is uncertain.
- Professional societies (ie, British Society of Gastroenterology (BSG)/European Society of Gastrointestinal Endoscopy (ESGE)) have recently issued practice guidelines that are mainly based on drug-specific pharmacokinetic properties, but outcome data on their safety and efficacy are still lacking.

What are the new findings?

- The very low rates of thromboembolic events observed in this prospective cohort supports the temporary short interruption of DOACs before GI endoscopy as recommended by the BSG/ESGE guidelines.
- When adhering to the BSG/ESGE guidelines, the risk of intraprocedural and delayed bleeding for therapeutic procedures, such as endoscopic mucosal resection, remains high. However, deviations from the BSG/ESGE recommendations tend to result in higher or not reduced risk of bleeding.
- Heparin bridging results in a substantial increase in the risk of delayed bleeding, supporting the BSG/ESGE position against this strategy.

How might it impact on clinical practice in the foreseeable future?

- The favourable benefit/risk ratio of the BSG/ESGE guidelines on periendoscopic management of DOACs supports their implementation into clinical practice.

Oral anticoagulants that directly inhibit thrombin (dabigatran etexilate) and factor Xa (apixaban, edoxaban and rivaroxaban) have become widely used since their approval as an alternative to vitamin K antagonists (VKAs) for prevention of

stroke in patients with non-valvular atrial fibrillation (NVAF)[1–3] and treatment and secondary prevention of venous thromboembolism (VTE).[4 5] As their use is rapidly expanding, the periprocedural management of patients who are receiving these drugs has become a common clinical problem; it is estimated that annually around 10%–15% of all patients on direct oral anticoagulants (DOACs) require their temporary interruption because of surgery or any invasive procedure.[6 7]

DOACs are characterised by a rapid onset and offset of action, short half-life and predictable anticoagulant effect at fixed dosing. These features could potentially simplify the periprocedural management of anticoagulation compared with VKAs, shortening the interval of drug interruption and obviating the costs and inconveniences of parenteral unfractionated or low-molecular-weight heparin (LMWH) bridging therapy. Nevertheless, the management of such patients is challenging, because evidence-based data to guide the optimal periprocedural timing of interruption and resumption of DOACs are still lacking. Moreover, routine laboratory tests, such as the prothrombin time and activated partial thromboplastin time, have inadequate sensitivity for the quantitative assessment of the anticoagulant activity of DOACs, and drug-specific assays to measure plasma concentration are not widely available.[8] This can be a major concern in any clinical situation in which assessing the intensity of anticoagulation is helpful, such as bleeding patients and those scheduled for a high-risk procedure or intervention.

Guidelines for the periendoscopic management of DOAC-treated patients are now available,[9–11] but they primarily reflect experts' opinions and are mainly based on drug-specific pharmacokinetic properties. Clinical data are urgently needed to provide a reliable estimate of the risk/benefit ratio of these recommendations so that they can be validated or updated. To our knowledge, only one prospective study has assessed a standardised perioperative management approach in patients scheduled for an elective surgery/procedure, but this study was limited as it included only dabigatran patients and a small number of endoscopy procedures at high bleeding risk, all represented by snare polypectomies.[12]

In this large multicentre prospective study, we aimed to assess the rate of adverse events with different strategies for periprocedural DOAC management and with adherence to the joint British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines.

METHODS

This multicentre prospective cohort study was conducted in 13 open-access GI endoscopy centres in Italy. The protocol was discussed in two meetings held in Turin among the principal investigators of each participating centre; the final version was approved by the institutional review boards and was registered in the http://www.clinicaltrials.gov register (NCT02734316).

All patients provided written informed consent. This was a no-profit study, and the manufacturers of oral direct anticoagulants were not involved in the study.

Study patients

The target population included all adult (≥18 years old) inpatients and outpatients on long-term anticoagulation with DOACs (dabigatran etexilate, apixaban, edoxaban and rivaroxaban) for any therapeutic indication and scheduled for elective GI endoscopy, either diagnostic or therapeutic.

Exclusion criteria were: (1) need for urgent endoscopy, regardless of indication (ie, acute GI bleeding, cholangitis and acute GI tract obstruction); (2) inability or unwillingness to provide informed consent; (3) cognitive impairment or psychiatric illness that might preclude reliable postprocedure follow-up and documentation of outcome events; and (4) previous participation in this study for the same procedure.

Table 1 Periendoscopic management of DOACs according to BSG/ESGE guidelines

	Low-risk procedures		High-risk procedures	
	Timing of last dose before endoscopy	Timing of first dose after endoscopy	Timing of last dose before endoscopy	Timing of first dose after endoscopy
Dabigatran etexilate (CrCl* >50 mL/min)	Evening of day −1	Evening of day of procedure	Morning of day −2 or evening of day −3	Day +2†
Dabigatran etexilate (CrCl 30–50 mL/min)	Evening of day −1	Evening of day of procedure	Morning of day −3 or evening of day −4	Day +2†
Apixaban	Evening of day −1	Evening of day of procedure	Morning of day −2 or evening of day −3	Day +2†
Rivaroxaban	Day −1	Same day of procedure	Day −3	Day +2†
Edoxaban	Day −1	Same day of procedure	Day −3	Day +2†

*CrCl=creatinine clearance, calculated by Cockcroft-Gault equation.
†Day+3 for procedure at very high risk of bleeding (large EMR, ESD), at endoscopist's discretion.
BSG, British Society of Gastroenterology; DOACs, direct oral anticoagulants; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ESGE, European Society of Gastrointestinal Endoscopy.

Study protocol and data recording

According to the non-interventional design of the study, the investigators did not adopt any prespecified protocol for the periprocedural management of the oral anticoagulant. The decision on continuing or stopping the anticoagulant before the endoscopic procedure and, where present, the timing of interruption was left to the discretion of the local study site or the referring physician.

On the day of endoscopy, eligible patients who were recruited by the investigators taking part in the project (one or two for each centre) were consecutively enrolled. Detailed demographic, clinical and procedural data were collected and entered into a web-based electronic platform. Creatinine clearance was calculated using the Cockcroft-Gault equation for any patient with serum creatinine performed within 30 days available.[13] After the procedure, patients were contacted by telephone (or visited, for inpatients still in hospital) after 1 week and 1 month and were interviewed about any adverse events and/or hospital admission. Follow-up data were double-checked by searching hospital records. The follow-up ended at 1 month in accordance with the recommendations of the International Society on Thrombosis and Haemostasis (ISTH).[14] The endoscopy procedures were stratified into low or high risk of bleeding according to the BSG/ESGE definition.[9]

The details on DOAC management, including the timing of the last dose intake before endoscopy and the timing of the first dose postprocedure, the use of heparin bridging before and/or after endoscopy and the specialty of the physician who provided the indication on pre-endoscopic anticoagulant management, were recorded. The length of interruption of anticoagulant therapy before and after the procedure was calculated for each

procedure and was compared with the BSG/ESGE recommendations (table 1) in order to differentiate between those which were and were not managed in adherence with these guidelines. Briefly, for low-risk endoscopic procedures, the BSG/ESGE guidelines suggest simply omitting the morning dose of DOAC on the day of the procedure and resuming the drug the same evening. For high-risk endoscopic procedures, they recommend discontinuing DOACs at least 48 hours prior to endoscopic procedures, except for dabigatran patients with impaired renal function (creatinine clearance of 30-50mL/min), for whom it is recommended to take the last dose 72 hours before. DOAC resumption is recommended about 48 hours after a high-risk procedure (ie, 2 days after endoscopy), except for procedures with a significant risk of delayed haemorrhage such as large endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), for which a longer period of discontinuation (72 hours; ie, 3 days after endoscopy) may be considered at the discretion of the endoscopist.

Patient stroke risk was calculated for each NVAF patient by means of the CHA_2DS_2-VASc score.[15] According to the American College of Chest Physician guidelines, VTE patients were classified at high risk of recurrence if the event (eg, deep vein thrombosis and pulmonary embolus) occurred within 3 months or there was a history of VTE associated with severe thrombophilia (deficiency of protein C, protein S or antithrombin; antiphospolipid antibodies syndrome; and multiple thrombophilic abnormalities), at intermediate risk if the event occurred in the preceding 3–12 months or there was a concomitant active cancer (ie, cancer treated within 6 months or managed with palliative care) and at low risk if the event occurred more than 12 months before and no other risk factors were present.[16]

Study outcomes

The primary outcome was the incidence of major and clinically relevant non-major bleeding (CRNMB) events, occurring either during endoscopy (intraprocedural bleeding) or within 30 days (delayed bleeding). Major GI bleeding events were defined by ≥1 of the following ISTH[17] criteria, adapted to the GI endoscopy setting: (1) bleeding that is fatal, (2) bleeding sufficiently large to cause haemodynamic instability associated with a drop in haemoglobin ≥20 g/L or transfusion of ≥2 units whole blood or red cells and (3) bleeding that leads to reintervention (eg, repetition of endoscopy, with or without haemostasis) or prolonged hospitalisation. CRNMB events were defined as those not satisfying the criteria for major bleeding but requiring medical intervention and an increased level of care (ie, prolonged monitoring and observation for intraprocedural events and unscheduled visit to the doctor's office or to an emergency department, but not hospital admission, for delayed events).[18]

Secondary outcomes were: (i) the incidence of thromboembolic arterial events (ischaemic stroke, systemic embolism and transient ischaemic attack) and venous events (symptomatic deep vein thrombosis or pulmonary embolism), confirmed by objective imaging studies and (2) the incidence of major and CRNMB events in patients managed according to the BSG/ESGE recommendations.

As intraprocedural bleeding is a common event during endoscopy, for the purpose of the study, we recorded only those requiring endoscopic haemostasis and/or other interventions that may prolong the length of the procedure, increase its difficulty and increase procedure-related costs. For high-risk procedures, the decision to endoscopically treat the site of bleeding was left to the clinical judgement of the endoscopist. Conversely, for bleeding occurring after biopsies (usually self-limiting and not requiring any active intervention), the participants agreed to have it endoscopically treated if the bleeding persisted over 3 min of observation.

Any recorded intraprocedural bleeding was classified as an CRNMB event according to the above-mentioned definitions.

Sample size and statistical analysis

We estimated that endoscopy-related major and CRNMB events occurred in 10%–15% of high-risk procedures in patients withholding anticoagulant therapy[19] and 0.1%–0.5% of low-risk endoscopic procedures. We also estimated a prevalence of 40% and 60% of high-risk and low-risk procedures, respectively. Thus, we hypothesised six possible scenarios, with a prevalence of bleeding after all endoscopic procedures ranging from 5% to 10% and a precision of 2.5% with 95% CI (online supplementary table 1). At interim analysis, we noticed a major bleeding occurrence of around 8%, so we estimated a sample size of at least 453 patients, increased to at least 500 patients after accounting for a 10% dropout rate, to assess a bleeding rate of 8% with 2.5% precision at 95% CI.

At the end of the enrolment period, we noticed that not all patients were given indications on the timing of DOAC interruption and resumption after endoscopy in accordance with the ESGE guidelines. On post hoc analysis, our sample had an 80% power to detect a risk difference in intraprocedural bleeding, between patients delaying DOAC interruption and subjects following the ESGE guidelines, of 11.5% after all procedures, 25.8% after high-risk procedures and 17.7% after low-risk procedures. However, we had an 80% power to estimate a risk difference in delayed bleeding rate in patients following the ESGE guidelines versus subjects who resumed DOAC earlier of 26.5% after high-risk procedures.

Categorical data are presented as proportions and associated with a 95% CI, whereas continuous data are reported as mean and SD or, in the case of skewed distribution, as median and IQR. Fisher's exact test with Bonferroni correction for multiple comparisons was used to compare outcome rates across patient subgroups. All statistical tests were two sided and were considered statistically significant at $p<0.05$. Analyses were done with STATA V.13 for Mac OS X.

RESULTS

Between March 2016 and June 2017, 552 consecutive patients undergoing elective GI endoscopic procedures were recruited; six patients declined consent and 17 were not enrolled because of physician's choice (patient's poor health and/or compliance). The remaining 529 patients (497 NVAF and 32 VTE patients) were included in the analysis; their demographic and clinical characteristics are presented in table 2. The median CHA_2DS_2-VASc score of NVAF patients was 3 (IQR 1–4); of the VTE patients, 3 were categorised at high, 18 at medium and 11 at low thromboembolic risk.

Among the included patients, 327 (61.8%) and 202 (38.2%) underwent low and high bleeding risk procedures, respectively (table 3).

The median time of anticoagulation interruption before the procedure was 1 day (IQR 0.5–2.5, range 0–4) and 3 days (IQR 2.5–4, range 1–5) for low-risk and high-risk procedures, respectively. The median time from procedure to anticoagulation resumption was 0 (same day of the procedure) (IQR 0–1, range 0–3) and 2 days (IQR 1–4, range 1–8).

Table 2 Demographic and clinical characteristics of study population

Characteristics	
Number of patients (%)	529–100
Male sex, n (%)	301–56.9
Age, mean (SD)	74.5–8.8
Body weight, kg, mean (SD)	74.6–15.2
Outpatients, n (%)	386–73
Indication for anticoagulation:	
Atrial fibrillation, n (%)	497–93.9
Venous thromboembolism, n (%)	32–6.1
Type of DOAC and maintenance dose	
Dabigatran 150 mg twice daily, n (%)	66–12.5
Dabigatran 110 mg twice daily, n (%)	73–13.8
Apixaban 5 mg twice daily, n (%)	105–19.9
Apixaban 2.5 mg twice daily, n (%)	66–12.4
Rivaroxaban 20 mg, n (%)	143–27
Rivaroxaban 15 mg, n (%)	67–12.7
Edoxaban 60 mg, n (%)	6–1.1
Edoxaban 30 mg, n (%)	3 (0,6)
Concomitant medications:	
Aspirin	27–5.1
P2Y12 inhibitors (clopidogrel, ticlopidina)	8–1.5
Creatinine clearance, mL/min, n (%)*	
<30	3–0.6
>30–<50	99–18.7
>50–<80	156–29.5
>80	208–39.3
Not available	63–11.9

DOAC, direct oral anticoagulant.

Among patients undergoing high-risk procedures, 30 patients (28 with AF and 2 with DVT at medium risk) received therapeutic-dose LMWH bridging. Of these, three patients were given LMWH both before and after the procedure; conversely 15 and 12 received it either before or after the procedure, respectively. The median CHA_2DS_2-VASc score of NVAF patients receiving bridging was 3 (IQR 1–4), comparable with that of patients who were not bridged.

Bleeding

Overall, there were 45 (8.5%; 95% CI 6.3% to 11.2%) major or CRNMB events. Of these, 28 occurred during the procedure (intraprocedural events) and 17 after patient discharge (delayed events). In detail, incidence of bleeding events was 1.8% (95% CI 0.7% to 45) and 19.3% (95% CI 14.1% to 25.4%) in low-risk and high-risk procedures, respectively.

Intraprocedural bleeding events were reported in 4/327 (1.2%, 95% CI 0.3 to 3.1) and 24/202 (11.9%, 95% CI 7.8 to 17.2) patients during low-risk and high-risk procedures, respectively ($p<0.001$). All bleeding events during low-risk procedures occurred in patients undergoing biopsies (biopsy mapping for staging of chronic gastritis in three patients; multiple biopsies on gastric ulcer suspected for malignancy in one patient), accounting for a bleeding risk after biopsies of 2.6% (4/152). Intraprocedural bleeding events during high-risk procedures occurred after EMR (12 cases; 11 colonic and 1 gastric), snare polypectomies (nine cases; eight colonic and one gastric), biliary sphincterotomy (one case), gastric ESD (one case) and pneumatic dilation (one case). All these events were successfully managed endoscopically and none fulfilled the criteria for major bleeding, so they were classified as CRNMB.

Delayed bleeding events were reported in 2/237 (0.6%, 95% CI 0.2% to 2.2%) patients during low-risk procedures (both including multiple biopsies for gastric mapping for chronic gastritis and follow-up of gastric low-grade lymphoma) and 15/202 (7.4%, 95% CI 4.2% to 12.0%) patients during high-risk procedures (seven colonic EMR, seven colonic snare polypectomies and one biliary sphincterotomy) ($p=0.01$). All these events fulfilled the criteria for major bleeding and were classified accordingly. They were managed case by case, as summarised in online supplementary table 2, and no death occurred.

Thromboembolic complications

In the total cohort of patients, there were 2 (0.4%, 95% CI 0% to 1.4%) thromboembolic events, both represented by transient ischaemic attack, characterised by transient focal neurological deficit with no evidence of acute infarction on brain CT scan. Both occurred in NVAF patients at high risk for thromboembolic complications, one 2 days after a low-risk procedure and the other 3 days after a high-risk procedure (online supplementary table 3).

Table 3 Number of endoscopic procedures, stratified by bleeding risk

Low-risk procedure, n (%)		High-risk procedure, n (%)	
Diagnostic upper or lower endoscopy, without biopsy*	161 (49.2)	Snare polypectomy†	111 (54.9)
Diagnostic upper or lower endoscopy, with biopsy (single site)‡	51 (15.7)	EMR§	48 (23.8)
Diagnostic endoscopy with biopsy (multiple sites)¶	101 (30.9)	ESD**	4 (2.0)
Diagnostic EUS††	7 (2.1)	ERCP with sphincterotomy	19 (9.4)
ERCP* without sphyncterotomy	7 (2.1)	EUS-guided tissue sampling	11 (5.4)
		PEG/PEJ	5 (2.5)
		Miscellaneous††	4 (2.0)
Total	327 (100)	Total	202 (100)

*Sixty-two oesophagogastroduodenoscopies, 96 colonoscopies, 3 device-assisted enteroscopies.
†Five gastric, 106 colorectal.
‡Twenty-one oesophagogastroduodenoscopies, 29 colonoscopies, 1 device-assisted enteroscopy.
§Four gastric, 44 colorectal.
¶Sixty-three oesophagogastroduodenoscopies, 38 colonoscopies.
**Three gastric, one rectal.
††Two pneumatic dilations, 1 colonic stenting, 1 oesophageal stenting.
EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

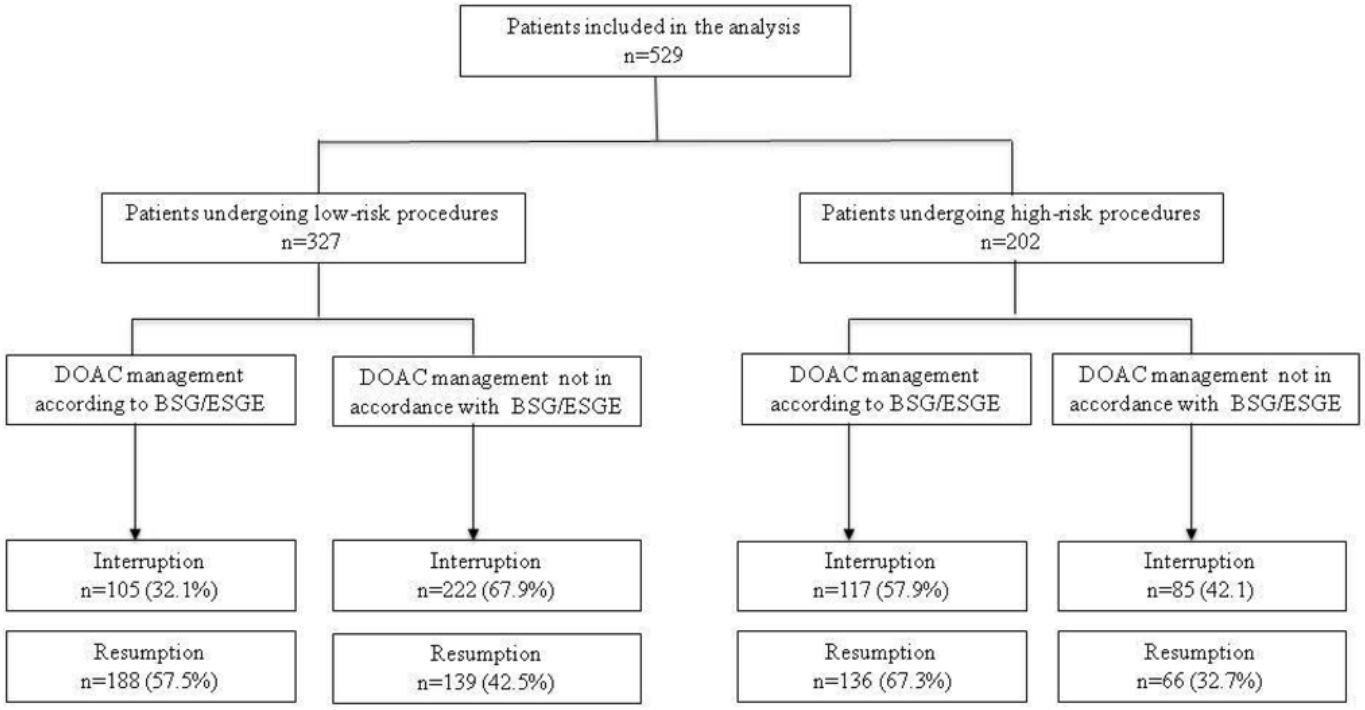

Figure 1 Study population stratified by procedure risk and DOAC management. BSG, British Society of Gastroenterology; DOAC, direct oral anticoagulant; ESGE, European Society of Gastrointestinal Endoscopy.

Risk of bleeding events according to the timing of anticoagulant interruption and resumption

The number of patients who were managed in accordance with the BSG/ESGE guidelines or deviated from them as concerns DOAC interruption and resumption are summarised in figure 1. Overall, DOAC interruption and resumption were managed in accordance with the BSGE/ESGE guidelines in 222 (41.9%) and 324 (61.25) patients, respectively.

The demographics, clinical characteristics and types of procedures were comparable between the two groups (online supplementary tables 4 and 5).

Adherence to the BSG/ESGE recommendations on the preprocedural DOAC interruption differed significantly according to the referring physician who provided the indication: 68.8% (115/150) for GI specialists, 40.1% (31/76) for cardiologists, 34.1% (30/88) for internists, 25.4 (26/102) for primary care physicians (PCPs), 21.2% for haematologists (11/52) and 14.8% for others (9/61) (p<0.001).

The incidence of clinically relevant intraprocedural bleeding stratified by the timing of the last dose taken before the procedure is reported in table 4. In high-risk procedures, 10.3% of patients who stopped anticoagulation according to the BSG/ESGE guidelines had intraprocedural bleeding, which was similar to those who stopped anticoagulation earlier (10.8%, p=0.99), but with a trend for a lower risk as compared with those with a shorter interruption of anticoagulation (ie, <48–72 hours) before the procedure (25%, p=0.07). In low-risk procedures, 0.9% of patients managed according to the BSG/ESGE guidelines had intraprocedural bleeding, comparable with those who stopped anticoagulation earlier (0.6%, p=0.99), and lower than subjects who continued anticoagulation (ie, did not skip the morning dose) (4%, p=0.24). When restricting the analysis of intraprocedural bleeding to the cohort of 152 patients undergoing low-risk procedures with biopsies, 38 patients did not skip the morning dose of DOAC; of these, two experienced intraprocedural bleeding requiring endoscopic haemostasis. Thus, the risk of intraprocedural bleeding was three times higher in the group of patients who continued DOACs (2/38, 5.2%) than in those who withheld the anticoagulant (2/114, 1.7%) (p=0.23).

The incidence of major delayed bleeding, stratified by the timing of the first dose resumed after the procedure, is reported in table 5. For high-risk procedures, this incidence was 6.6% in patients managed according to the BSG/ESGE guidelines, and 7.7% in patients with delayed resumption of anticoagulation (6.6% vs 7.7%) (p=0.76), but almost twice as high in patients with resumption of anticoagulation earlier than recommended by the BSG/ESGE guidelines, though only a non-significant trend was observed (14.3% vs 6.6%, p=0.27). For low-risk procedures, the incidence of delayed major bleeding was 0.5%

Table 4 Risk of major or clinically relevant non-major intraprocedural bleeding according to the timing of direct oral anticoagulant interruption

	Patients with intraprocedural bleeding according to the last dose before procedure			
	As recommended	Earlier	Later	Overall
Low-risk procedures n/N (%) (95% CI)	1/105 (0.9) (0 to 5.4)	1/172 (0.6) (0 to 3.2)	2/50 (4) (0.5 to 13.7)	4/327 (1.2)* (0.4 to 3.2)
High-risk procedures n/N (%; 95% CI)	12/117 (10.3) (5.4 to 17.2)	7/65 (10.8) (4.4 to 20.9)	5/20 (25) (8.7 to 49.9)	24/202 (11.9)* (8.1 to 17.1)

*All the events were clinically relevant non-major bleeding events.

Table 5 Risk of delayed major bleeding according to the timing of direct oral anticoagulant resumption

	Patients with delayed bleeding according to the first dose after procedure			
	As recommended	Later	Earlier	Overall
Low-risk procedures n/N (%) (95% CI)	1/188 (0.5) (0 to 2.9)	1/139 (0.7) (0 to 3.9)	–	2/327 (0.6) (0.1 to 2.2)
High-risk procedures n/N (%) (95% CI)	9/136 (6.6) (3.1 to 12.2)	4/52 (7.7) (2.1 to 18.5)	2/14 (14.3) (1.8 to 42.8)	15/202 (7.4) (4.6 to 11.9)

in patients managed according to the BSG/ESGE guidelines and 0.7% in patients who resumed anticoagulation later (p=0.88).

Periprocedural bridging anticoagulation and risk of bleeding

Among patients undergoing high-risk procedures and receiving bridging anticoagulation, four experienced intraprocedural bleeding and four delayed major bleeding. Intraprocedural bleeding occurred in 4/18 (22.2%; 95% CI 6.4% to 47.6%) patients receiving bridging before endoscopy versus 20/184 (10.9%; 95% CI 6.8% to 16.3%) in patients who did not (p=0.24). As concerns delayed major bleeding, the incidence was 4/15 (26.7%; 95% CI 7.8% to 55.1%) and 11/187 (5.9%; 95% CI 3.0% to 10.3%) in bridged and non-bridged patients, respectively (p=0.017).

DISCUSSION

The present study represents the first prospective evaluation of clinical outcomes associated with periprocedural management of DOACs in patients undergoing elective GI endoscopic procedures. The study shows an overall very low rate of thromboembolic events, suggesting that a temporary short interruption of these drugs, related to their pharmacokinetic properties, is effective in minimising thromboembolic events. However, the risk of clinically relevant bleeding events is substantial when high-risk endoscopic procedures are performed, even in patients managed in accordance with guideline recommendations. Nevertheless, our results support the validity of the BSG/ESGE recommendations, as possible deviations tend to result in a higher or not reduced risk of bleeding.

The results of our study are relevant for a number of reasons. First, most of the intraprocedural bleeding episodes—accounting for more than half of all the bleeding episodes—were successfully managed during endoscopy, with no additional burden or risk to patients. Interestingly, an interval of DOAC interruption before high-risk procedures longer than recommended by the BSG/ESGE guidelines, theoretically exposing patients to a higher risk of thromboembolic complications, did not appear to reduce the risk of intraprocedural bleeding. This finding supports the BSG/ESGE recommendations on the timing of preprocedure DOAC interruption for high-risk procedures.

Second, the risk of intraprocedural bleeding is not negligible in low-risk procedures with biopsies. Thus, the BSG/ESGE suggestion to omit the morning dose of DOACs on the day of the procedure so that biopsies can be sampled at a trough level (ie, 12 or 24 hours after the last drug intake) appears reasonable. We believe that a 5.2% risk of clinically relevant intraprocedural bleeding after biopsies in patients who did not omit the morning dose, balanced with the negligible risk of thromboembolic events for this very short period of drug interruption, deserves a critical reassessment of American Society for Gastrointestinal Endoscopy[10] and the joint Asian Pacific Association of Gastroenterology and Asian Pacific Society for Digestive Endoscopy guidelines,[11] which recommend to continue anticoagulation in case of low-risk procedures. Again, as clinically relevant intraprocedural bleeding occurred in about 3% of the procedures after biopsy mapping (ie, biopsies in multiple sites), greater awareness should be reserved to these patients, and a possible reassessment of the guidelines for this subgroup of patients may be considered.

Third, the risk of delayed bleeding—likely to result in additional exploitation of medical and economic resources—was sensitive to the time of resumption of DOAC therapy. In particular, any anticipation as compared with the BSG/ESGE recommendations tended to result in a higher bleeding risk, and it should be strongly discouraged. We consider this difference to be of high clinical impact, although statistical significance was not achieved, as it was lower than the needed 26.5% risk difference, calculated post hoc based on our study sample. However, delayed resumption did not result in a decreased risk of bleeding. This finding was not unexpected, as it is well known that delayed bleeding in patients taking anticoagulants may occur several days after the procedure.[19] Of note, half of the delayed bleeding events complicating EMR procedures occurred within 2 days when DOAC was resumed 48 hours after endoscopy. Taken all together, these findings support the BSG/ESGE protocol for postprocedure DOAC resumption, and they strengthen the suggestion of the BSG/ESGE guidelines to consider a longer period of DOAC discontinuation (72 hours) for procedures at very high risk of delayed haemorrhage, particularly in patients in a relatively low thrombotic risk category.

Fourth, we showed the unsafety of heparin bridging in DOAC patients, consistent with data from post hoc analysis of randomised trials, observational registries[20 21] and a recent large nationwide database analysis.[22] However, with the overall very low rates of thromboembolic events, it is not conceivable that heparin bridging could significantly impact thromboembolic risk, as already demonstrated for warfarin patients.[23] When considering the lack of effect of such bridging on the thromboembolic risk, the risk/benefit of such intervention appears unsuitable for clinical practice. Noteworthy, we observed a comparable median CHA_2DS_2-VASc score between NVAF patients who were given heparin bridging and those who were not. Thus, it is conceivable that the use of LMWH bridging more likely reflects a scarce knowledge of the guidelines rather than a perceived higher risk of thromboembolism.

The present study has several strengths. First, the prospective design and the precise assessment of periendoscopic timing of drug interruption and resumption make our study the first of its kind. Recently, a large nationwide retrospective study demonstrated that among 5000 propensity-matched pairs of warfarin and DOAC users, DOAC use was associated with a modest but significantly lower postprocedure bleeding risk compared with warfarin.[22] However, this study did not provide any useful information for the clinician regarding the optimal periendoscopic management of these drugs, as data on the timing of anticoagulant cessation and resumption were

missing. Second, we focused on endoscopic procedures only, and we included all DOACs licenced on the marketplace, and this differentiates our study from the prospective cohort study on perioperative management of dabigatran published by Schulman *et al*.[12] Third, all major or CRNMB events were identified by endoscopy reports or hospital admission charts, so that they could be objectively recorded and correctly classified according to the study protocol.

We also acknowledge some limitations. First, from a study design standpoint, randomised trials remain the methodological reference standard to investigate pharmacological or other management interventions. However, we believe that the prospective cohort design used in our study is also appropriate, as the expected risk of clinical events is low. Interestingly, in our study, comparisons between different management strategies could be made by the presence of a control group, represented by patients not managed in accordance with the guidelines. We recognise that these comparisons must be cautiously considered, as no study sample size was predefined and most of the analyses provided speculative data but are underpowered to draw firm conclusions. In addition, caution should be given to generalisability of study findings when the ESGE/BSG guidelines are to be implemented, as adherence in our study was variable. Second, due to the study design, we cannot definitely exclude the possibility of reporting bias, as the timing of DOAC interruption and resumption and other clinical features (ie, heparin use) were self-declared by patients. Third, we cannot exclude a selection bias as it concerns patient enrolment; however, participation in the study by only one or two investigators for each centre, who were highly motivated in patient recruitment, should have minimised any bias. Moreover, the inclusion of patients at low to high thromboembolic risk and of procedures with low to very high bleeding risk suggests that the selection bias was marginal. Lastly, the anticoagulant activity of the DOACs before the procedure or in the case of delayed bleeding complication was not routinely assessed during the study.

In conclusion, the results of our large prospective study suggest that in patients on DOACs undergoing elective GI endoscopy, the risk of major or clinically relevant non-major bleeding events is considerable. In particular, high-risk procedures seem to be associated with a substantial risk of delayed major bleeding, which varies according to the type of procedure. Routine perioperative bridging with heparin substantially increases the risk of bleeding without providing any clinical benefit to these patients. Short-term interruption of anticoagulation, as recommended by the BSG/ESGE guidelines, appears to be a safe and effective strategy for containing bleeding events and minimising thromboembolic risk.

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Correction: *periendoscopic management of direct oral anticoagulants: a prospective cohort study*

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The last two lines of the results section of the abstract should read:

The incidence of delayed bleeding appeared similar in patients who resumed anticoagulation according to BSG/ESGE guidelines or later (6.6% vs 7.7%, p=0.76), but it tended to increase when DOAC was resumed earlier (14.3% vs 6.6%, p=0.27). The risk of delayed major bleeding was significantly higher in patients receiving heparin bridging than in non-bridged ones (26.7% vs 5.9%, p=0.017).

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