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ORIGINAL ARTICLE

Clinical significance of gastrointestinal bleeding history in patients who undergo left atrial appendage closure

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Abstract

Background and Aim: Anticoagulant users with nonvalvular atrial fibrillation (NVAF) sometimes suffer from gastrointestinal bleeding (GIB) and have difficulty continuing the medication. Left atrial appendage closure (LAAC) has been developed for such situations. We aimed to clarify the clinical significance of a history of GIB in comparison to other factors in patients who had undergone LAAC.
Methods: From October 2019 to September 2023, patients with NVAF who underwent LAAC at our hospital were enrolled. We investigated the percentage of patients with a history of GIB who underwent LAAC and compared the incidence of post-LAAC bleeding in these patients compared to those with other factors.
Results: A total of 45 patients were included. There were 19 patients (42%) with a history of GIB who underwent LAAC. In a Kaplan–Meier analysis, the cumulative incidence of bleeding complications after LAAC was significantly higher in patients with a history of GIB in comparison to patients with other factors. There were eight cases of post-LAAC bleeding in total, and seven cases had GIB.
Conclusions: We need to recognize that GIB is a significant complication in patients who undergo LAAC. The management of GIB by gastroenterologists is essential to the success of LAAC.

Introduction

The incidence of atrial fibrillation is increasing with aging of the population.[1] Among patients with nonvalvular atrial fibrillation (NVAF), anticoagulant therapy with agents such as warfarin (WF) or direct oral anticoagulants (DOACs) is recommended for the prevention of cardiogenic and cerebral embolisms.[2,3] However, some patients may suffer from hemorrhagic complications due to anticoagulant therapy. Gastrointestinal bleeding (GIB) is the most common type of major bleeding in patients receiving oral anticoagulants.[4,5] The subsequent resumption of anticoagulant therapy after GIB is mandatory because longer cessation of anticoagulants leads to higher mortality. On the other hand, earlier resumption of anticoagulant therapy leads to a higher risk of recurrent bleeding.[6]

Left atrial appendage closure (LAAC) has been developed for such unmet medical needs in clinical practice. Based on the PROTECT AF and PREVAIL clinical trials, there has been evidence to support the noninferiority of the LAAC device for stroke prevention in comparison to WF.[7,8] More recently, it has also been reported that the EWOLUTION registry in Europe combined with the results of a 5-year follow-up from both the PROTECT AF and PREVAIL trials demonstrated not only the noninferiority but also a reduced risk of hemorrhagic stroke in comparison to WF.[7–10] Since anticoagulant therapy is no longer necessary for patients who undergo LAAC, it can reduce not only the risk of embolism but also the risk of major bleeding, including GIB. The incidence of bleeding events after LAAC has been reported to range from 2.2% to 10% per year.[11–13] For GIB, a prior study identified a history of GIB as a predictor of bleeding events after LAAC.[14] However, the differences in the clinical course and complications during the perioperative period of LAAC between patients with a history of GIB and other patients have not been fully studied. In this study, we aimed to elucidate the difference in clinical outcomes between patients who underwent LAAC with a history of GIB in comparison to other patients.

Methods

Study population. This was a single-center, retrospective observational study. From October 2019 to September 2023,

patients of ≥20 years of age with NVAF who underwent LAAC at our hospital were enrolled. Ultimately, 45 patients were included in this study.

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Okayama University, and informed consent was obtained with the opt-out facility.

Indication for left atrial appendage closure. Patients with NVAF who have a history of major bleeding or diffuse amyloid angiopathy, have a HAS-BLED score ≥3, and who need to take two or more antiplatelet agents for more than 12 months are recommended to undergo LAAC.[15] Indication for LAAC was defined as meeting one or more of the above conditions.

LAAC procedure, postprocedural antithrombotic therapy, and follow-up assessment. LAAC was performed under general anesthesia with transesophageal echocardiography (TEE) guidance. LAAC could be performed by either of the available percutaneous techniques used in our institution, namely Watchman or Watchman FLX (Boston Scientific, Natick, MA, USA). Patients received regular checkups at 1.5, 3, and 6 months after LAAC. Planned left atrial imaging with transthoracic echocardiography or TEE and cardiac computed tomography was performed. The standardized postprocedural antithrombotic therapies are WF and single-antiplatelet therapy (SAPT) for 1.5 months, dual-antiplatelet therapy (DAPT) for 6 months after the documentation of satisfactory LAAC (peri-device leak <5 mm), or lifetime aspirin therapy.[7,16–18] Direct oral anticoagulation (DOAC) is also considered a feasible alternative to WF for the initial period. Since it usually takes approximately 1.5 months for the LAAC device to be covered with endothelial cells, patients need to take anticoagulants plus aspirin during that period. After confirmation that the LAAC device was covered with endothelial cells at 1.5 months after LAAC, the physician switched to DAPT, which means that anticoagulant therapy was no longer necessary.

Evaluations. We retrospectively reviewed the medical records, and the following baseline characteristics were collected for all patients: age, sex, comorbidities, estimated glomerular filtration (eGFR), CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female), as well as HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly) scores, antithrombotic medications during the perioperative period of LAAC, details of GIB, follow-up period, and complications.

The severity of bleeding events was assessed by the Bleeding Academic Research Consortium (BARC) classification. We defined major bleeding as BARC bleeding definition type ≥3.[19]

We investigated the difference in clinical characteristics and the incidence of post-LAAC bleeding between patients with a history of GIB and other patients. We also assessed the details of GIB history, details of rebleeding cases after LAAC, and antithrombotic regimens before and after LAAC.

Statistical analyses. Continuous variables are presented as the median and interquartile range (IQR) and were compared using the Mann–Whitney test. Categorical variables were presented as percentages and compared using Fisher's exact test. The Kaplan–Meier method was used to compare the incidence of rebleeding after LAAC between patients with a history of GIB and other patients. All statistical analyses were performed using the JMP Pro software program, version 15.0 (SAS Institute, Cary, NC, USA). *P*-values <0.05 were considered to indicate statistical significance.

Results

Patient characteristics. Table 1 shows the clinical characteristics of patients who underwent LAAC because of a history of GIB and others. There were 19 patients (42%) with a history of GIB among those who underwent LAAC. The median age of the patients with a history of GIB was lower than that of the other patients (77 years *vs* 72 years, $P = 0.015$). There were no significant differences in the percentage of patients who had a

Table 1 Clinical characteristics of patients who underwent left atrial appendage closure (LAAC) due to a history of gastrointestinal bleeding and those who underwent LAAC due to other reasons

	GIB ($n = 19$)	Others ($n = 26$)	*P*-value
Age, median, years (IQR)	77 (71–84)	72 (64–76)	0.015
Female, *n* (%)	11 (58)	16 (62)	1.0
HT, *n* (%)	15 (79)	19 (73)	0.74
DM, *n* (%)	8 (42)	9 (35)	0.76
CAD/PAD, *n* (%)	5 (26)	9 (35)	0.75
CVD/TIA, *n* (%)	8 (42)	5 (19)	0.11
eGFR, median, ml/min/1.73 m^2 (IQR)	46.5 (30.1–60.4)	54.4 (39.7–70.2)	0.21
CHA2DS2-VASc score, median (IQR)	4 (4–5)	3 (3–5)	0.042
HAS-BLED score, median (IQR)	3 (3–4)	3 (3–4)	0.24
NSAID users, *n* (%)	0	2 (7.7)	0.50

CAD, coronary artery disease; CVD, cerebrovascular disorder; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GIB, gastrointestinal bleeding; HT, hypertension; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral artery disease; TIA, transient ischemic attack.

history of hypertension, diabetes mellitus, cardiovascular disease, and nonsteroidal anti-inflammatory drug (NSAID) usage between the two groups. The median CHA2DS2-VASc score of the patients with a history of GIB was significantly higher than that of the other patients (4 *vs* 3, $P = 0.042$). The median HAS-BLED scores of the two groups did not differ to a statistically significant extent (3 *vs* 3, $P = 0.24$).

Details of gastrointestinal bleeding history leading to LAAC. Table 2 shows the details of the history of GIB leading to LAAC. The most common bleeding site was the colon (58.0%), followed by the stomach or duodenum (26.0%). With regard to the diagnosed source of bleeding, half of the patients had angioectasia, and the other patients had various diseases such as diverticular bleeding (16%), hemorrhagic ulcer (11%), obscure gastrointestinal bleeding (11%), gastric hyperplastic polyp (5.3%), radioactive enteritis (5.3%), and ischemic colitis (5.3%).

Postoperative complications of LAAC. Information about postoperative complications of LAAC is shown in Table 3. There was no significant difference in the median follow-up time after LAAC between patients with a history of GIB and the other patients (20.1 *vs* 18.5 months, respectively). Among the patients, eight (18.0%) experienced post-LAAC bleeding. The rate of post-LAAC bleeding was 32.0% in patients with a history of GIB and 3.8% in other patients. No procedural complications or thromboembolisms were observed in either group.

Table 2 Details of cases with a history of gastrointestinal bleeding leading to left atrial appendage closure

	Study population ($n = 19$)
Location	
Stomach or duodenum	5 (26)
Small intestine	1 (5.3)
Colon	11 (58)
Unknown	2 (11)
Primary disease	
Angioectasia	9 (47)
Diverticular bleeding	3 (16)
Hemorrhagic ulcer	2 (11)
Obscure gastrointestinal bleeding	2 (11)
Gastric hyperplastic polyp	1 (5.3)
Radioactive enteritis	1 (5.3)
Ischemic colitis	1 (5.3)

Post-LAAC bleeding in patients with a history of GIB and other patients. The results of the Kaplan–Meier analysis for rebleeding events after LAAC between patients with a history of GIB and other patients are shown in Figure 1. Patients with a history of GIB had a higher rate of rebleeding after LAAC in comparison to the other patients ($P = 0.0075$).

Clinical characteristics of post-LAAC bleeding cases. The clinical characteristics of post-LAAC bleeding cases ($n = 8$) are shown in Table 4. The indication for LAAC was GIB in seven cases and a high risk of bleeding due to liver cirrhosis in one case. The CHA2DS2-VASc and HAS-BLED scores tended to be higher in patients with rebleeding. The timing of rebleeding events ranged from 0.5 to 33.7 months after LAAC. The BARC score was 3a in seven cases and 3c in one case. The type of rebleeding was GIB in almost all cases ($n = 7$). Cerebral hemorrhage occurred in one case.

Antithrombotic regimen during the perioperative period of LAAC. Details of the antithrombotic regimen during the perioperative period of LAAC are shown in Table 5. There were many variations in clinical practice because physicians appropriately changed the antithrombotic regimen based on each patient's background. DOAC therapy was the predominant antithrombotic therapy before LAAC. From just after LAAC to 1.5 months after LAAC, the standard regimen was anticoagulant and SAPT, which was administered to approximately 50% of the patients. From 1.5 to 6 months after LAAC, the standard regimen (DAPT) was applied in 24/45 cases (53%). In most cases, anticoagulants were withdrawn during this period. At ≥6 months after LAAC, the standard regimen (SAPT) was applied in 37/45 cases (82%). From ≥1.5 months after LAAC, the details of antithrombotic therapy were unknown in three cases because they were followed up at other hospitals.

Discussion

In summary, we clarified the difference in the clinical course and outcomes between patients with a history of GIB and others who underwent LAAC. Among patients who underwent LAAC at our institution, 42% had a history of GIB, which means that a history of GIB is the most important symptom for the indication of LAAC. Moreover, the incidence of bleeding complications after LAAC was significantly higher in patients with a history of GIB than in other patients. GIB also accounted for the majority of bleeding after LAAC. We believe that gastroenterologists have a significant role not only in the management of bleeding

Table 3 Complications associated with left atrial appendage closure

	Total ($n = 45$)	GIB ($n = 19$)	Others ($n = 26$)
Follow-up period, median, months (IQR)	19 (12.4–32)	20.1 (12.5–35.1)	18.5 (12.1–26.6)
Procedural complications, *n*	0	0	0
Complications after LAAC			
GIB bleeding, *n* (%)	7 (16)	6 (32)	0
Stroke, *n* (%)	1 (2.2)	0	1 (3.8)
Thromboembolism, *n*	0	0	0

GIB, gastrointestinal bleeding; IQR, interquartile range; LAAC; left atrial appendage closure.

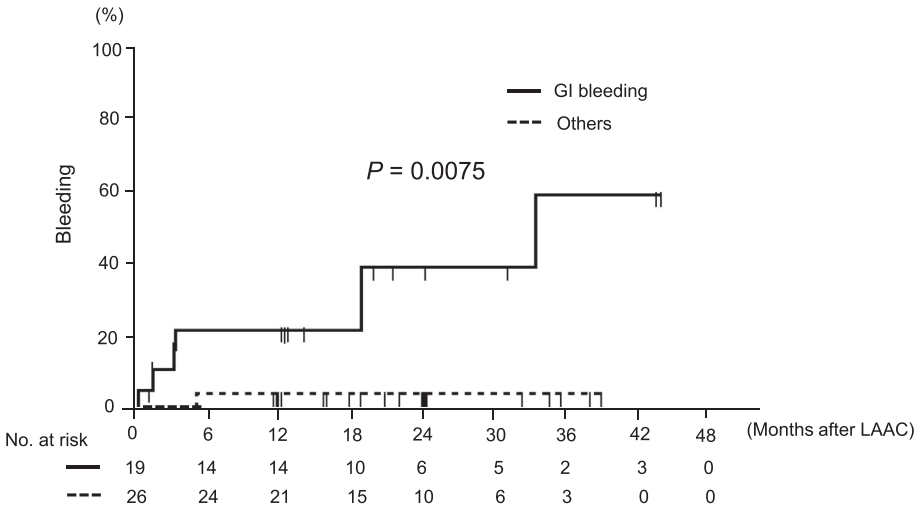

Figure 1 Kaplan–Meier curve for the cumulative risk of rebleeding after left atrial appendage closure between patients with a history of gastrointestinal bleeding and other patients. GIB, gastrointestinal bleeding; LAAC, left atrial appendage closure.

Table 4 Details of cases with rebleeding

Case	Age	Sex	Indication of LAAC	CHA2DS2-VASc	HAS-BLED	Timing of rebleeding (months after LAAC)	BARC	Types of rebleeding
1	78	M	GIB (colonic angioectasia)	8	6	19.1	3a	OGIB
2	69	F	GIB (OGIB)	4	3	19.1	3a	OGIB
3	84	F	GIB (colonic angioectasia)	4	3	33.7	3a	OGIB
4	87	F	GIB (GAVE)	5	3	3.6	3a	GAVE
5	59	M	Other (high risk of bleeding due to LC)	3	3	5.3	3a	Colonic diverticular bleeding
6	77	M	GIB (colonic diverticular bleeding)	6	4	0.5	3a	Colonic diverticular bleeding
7	68	M	GIB (colonic diverticular bleeding)	3	3	3.4	3a	Colonic diverticular bleeding
8	80	M	GIB (OGIB)	4	3	1.6	3c	Cerebral hemorrhage

F, female; GAVE, gastric antral vascular ectasia; GIB, gastrointestinal bleeding; LAAC, left atrial appendage closure; LC, liver cirrhosis; M, male; OGIB, obscure gastrointestinal bleeding.

complications during the perioperative period of LAAC but also in the great success of the LAAC procedure.

Most patients had been taking DOACs before LAAC in the present study. The proportion of new users of DOACs is increasing,[20] and it has been reported that DOAC users have a higher risk of lower GIB in comparison to WF users.[21] This may be explained by the local anticoagulant effects of DOACs.[22] This is why the most frequent bleeding site was the colon (58%) among the patients with a history of GIB who underwent LAAC in the present study. Regarding the primary disease, angioectasia was the most frequent (47%), which is in line with a previous report.[21] Sites of angioectasia are fragile and bleed easily, especially in anticoagulant users. In cases of gastrointestinal diseases for which LAAC is applicable, DOAC users with recurrent lower GIB may be good indications.

Our study showed that patients with a history of GIB who underwent LAAC had a higher risk of bleeding after LAAC in comparison to other patients. Moreover, GIB also accounted for most cases of bleeding after LAAC. GIB is mostly related to an underlying anatomical lesion that is not expected to be cured by LAAC, and only scarce data are available regarding the efficacy of LAAC (and oral anticoagulant discontinuation) in preventing the recurrence of GIB.[23] A history of GIB, especially lower GIB, was reported to be significantly associated with a higher risk of bleeding after LAAC.[24,25] In previous studies, a history of GIB was an indication for LAAC in a large percentage of the cases, and a higher rate of bleeding after LAAC (5.8–27.7%) was reported.[14,24,26,27] Even though the variety of antithrombotic therapy regimens based on the physician's judgment after LAAC might contribute to the differences in the bleeding rate, we need to recognize that patients with a history of GIB still have a higher risk of bleeding after LAAC.

Regarding the timing of bleeding after LAAC, the rate of bleeding was 56% within 3 months after LAAC, 19% at 3–

Table 5 Details of antithrombotic regimen during perioperative period of left atrial appendage closure

	Before LAAC	<1.5 months after LAAC	1.5–6 months after LAAC	>6 months after LAAC
DOAC	30	16	2	2
WF	6	2	1	1
SAPT	1	0	15	37
DOAC + SAPT	4	20	0	0
WF + SAPT	1	4	0	0
DOAC + DAPT	2	0	0	0
DAPT	1	3	24	2
Unknown	0	0	3	3

DAPT, dual antiplatelet; DOAC, direct oral anticoagulant; LAAC; left atrial appendage closure; SAPT, single antiplatelet; WF, warfarin.

12 months after LAAC, and 25% at ≥12 months after LAAC.[24] The incidence of bleeding complications is also known to be the highest during DAPT therapy after LAAC.[25] Since the severity of gastrointestinal mucosal injury tends to be higher in DAPT users than in aspirin or clopidogrel users,[28] close attention should be paid to GIB complications within 6 months after LAAC. However, in our study, three patients with GIB experienced rebleeding more than 12 months after LAAC. At present, SAPT therapy is recommended for more than 6 months after LAAC. Given that the bleeding risk persists for more than 12 months after LAAC in some cases, we need to further explore when to stop antithrombotic therapy after LAAC in the future.

How can we reduce the risk of rebleeding after LAAC in cases with a history of GIB? We suggest that modifying the antithrombotic regimen after LAAC could reduce the risk of rebleeding after LAAC in patients with a history of GIB. For instance, a retrospective study analyzed the safety and effectiveness of reduced-dose (rivaroxaban 15 mg daily) and half-dose DOAC therapy (rivaroxaban 10 mg daily) *versus* standard WF therapy.[29] Another study reported that the concomitant use of aspirin with DOACs did not reduce the risk of stroke or transit ischemic attack but increased the risk of adverse events.[30] Since the optimal antithrombotic strategy after interventional LAAC is controversial, further investigation should be conducted in the future.

This study had several limitations. First, the sample size was relatively small because this was a single-center, retrospective study. Second, the antithrombotic regimen after LAAC varied in each case because the physicians considered the risk of GIB based on the patient's background. As shown in Table 5, there were three cases in which anticoagulants were continued. Third, the median observation period was 19 months, which was relatively short compared to that in previous reports. A larger-scale, prospective observational study is warranted to solve these issues.

Conclusion

In conclusion, we should recognize that GIB is a significant disease that can be a candidate for LAAC. The risk of rebleeding after LAAC was significantly higher in patients with a history of GIB in comparison to other patients. Although we could reduce the risk of rebleeding after LAAC by modifying the antithrombotic regimen, the management of GIB by gastroenterologists is crucial for the success of LAAC.

References

1 Kotalczyk A, Lip GY, Calkins H. The 2020 ESC guidelines on the diagnosis and management of atrial fibrillation. *Arrhythm. Electrophysiol. Rev.* 2021; **10**: 65–7.

2 Cheng WH, Chiang CE, Lin YJ *et al*. Non-vitamin K antagonist oral anticoagulants in elderly (≥85 years) patients with newly diagnosed atrial fibrillation: changing clinical practice and outcomes for stroke prevention in a Nationwide Cohort Study. *Mayo Clin. Proc.* 2021; **96**: 52–65.

3 O UF, Chong TK, Wei Y *et al*. Clinical features and outcomes of patients in different age groups with non-valvular atrial fibrillation receiving oral anticoagulants. *Int. J. Cardiol. Heart Vasc.* 2022; **40**: 101009.

4 Granger CB, Alexander JH, McMurray JJ *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 2011; **365**: 981–92.

5 Giugliano RP, Ruff CT, Braunwald E *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 2013; **369**: 2093–104.

6 Staerk L, Lip GY, Olesen JB *et al*. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2015; **351**: h5876.

7 Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation*. 2011; **123**: 417–24.

8 Belgaid DR, Khan Z, Zaidi M, Hobbs A. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *Int. J. Cardiol.* 2016; **219**: 177–9.

9 Bergmann MW, Betts TR, Sievert H *et al*. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention*. 2017; **13**: 877–84.

10 Reddy VY, Doshi SK, Kar S *et al*. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J. Am. Coll. Cardiol.* 2017; **70**: 2964–75.

11 Freixa X, Gafoor S, Regueiro A *et al*. Comparison of efficacy and safety of left atrial appendage occlusion in patients aged <75 to ≥ 75 years. *Am. J. Cardiol.* 2016; **117**: 84–90.

12 Landmesser U, Tondo C, Camm J *et al*. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. *EuroInter vention*. 2018; **14**: e590–7.
13 Phillips KP, Santoso T, Sanders P *et al*. Left atrial appendage closure with WATCHMAN in Asian patients: 2 year outcomes from the WASP registry. *Int. J. Cardiol. Heart Vasc.* 2019; **23**: 100358.
14 López-Mínguez JR, Nogales-Asensio JM, Infante De Oliveira E *et al*. Major bleeding predictors in patients with left atrial appendage closure: the Iberian Registry II. *J. Clin. Med.* 2020; **9**: 2295.
15 Hindricks G, Potpara T, Dagres N *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* 2021; **42**: 373–498.
16 Holmes DR, Reddy VY, Turi ZG *et al*. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009; **374**: 534–42.
17 Holmes DR Jr, Kar S, Price MJ *et al*. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J. Am. Coll. Cardiol.* 2014; **64**: 1–12.
18 Aonuma K, Yamasaki H, Nakamura M *et al*. Percutaneous WATCHMAN left atrial appendage closure for Japanese patients with nonvalvular atrial fibrillation at increased risk of thromboembolism—first results From the SALUTE trial. *Circ. J.* 2018; **82**: 2946–53.
19 Mehran R, Rao SV, Bhatt DL *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011; **123**: 2736–47.
20 Perreault S, de Denus S, White-Guay B *et al*. Oral anticoagulant prescription trends, profile use, and determinants of adherence in patients with atrial fibrillation. *Pharmacotherapy*. 2020; **40**: 40–54.
21 Ingason AB, Hreinsson JP, Agustsson AS *et al*. Warfarin is associated with higher rates of upper but not lower gastrointestinal bleeding compared with direct oral anticoagulants: a population-based propensity-weighted cohort study. *Clin. Gastroenterol. Hepatol.* 2023; **21**: 347–357.e10.
22 Desai J, Kolb JM, Weitz JI, Aisenberg J. Gastrointestinal bleeding with the new oral anticoagulants—defining the issues and the management strategies. *Thromb. Haemost.* 2013; **110**: 205–12.
23 Lempereur M, Aminian A, Freixa X *et al*. Left atrial appendage occlusion in patients with atrial fibrillation and previous major gastrointestinal bleeding (from the Amplatzer Cardiac Plug Multicenter Registry). *Am. J. Cardiol.* 2017; **120**: 414–20.
24 Faroux L, Cruz-González I, Arzamendi D *et al*. Incidence, predictors, and clinical impact of bleeding recurrence in patients with prior gastrointestinal bleeding undergoing LAAC. *Pacing Clin. Electrophysiol.* 2021; **44**: 1216–23.
25 Zieliński K, Pracoń R, Konka M *et al*. Incidence and predictors of clinically significant bleedings after transcatheter left atrial appendage closure. *Int. J. Environ. Res. Public Health*. 2022; **19**: 13802.
26 Wintgens LIS, Vorselaars VMM, Klaver MN *et al*. Left atrial appendage closure in atrial fibrillation patients with prior major bleeding or ineligible for oral anticoagulation. *Neth. Heart J.* 2019; **27**: 613–20.
27 Aonuma K, Yamasaki H, Nakamura M *et al*. Efficacy and safety of left atrial appendage closure with WATCHMAN in Japanese nonvalvular atrial fibrillation patients—final 2-year follow-up outcome data from the SALUTE trial. *Circ. J.* 2020; **84**: 1237–43.
28 Shimada Y, Hojo M, Kita Y *et al*. Comparison of the degree of gastric mucosal injury between patients who are receiving dual antiplatelet therapy or single antiplatelet therapy. *Diagnostics (Basel)*. 2022; **12**: 2364.
29 Zhou XD, Chen QF, Lin F *et al*. Reduced- or half-dose rivaroxaban following left atrial appendage closure: a feasible antithrombotic therapy in patients at high risk of bleeding? *J. Clin. Med.* 2023; **12**: 847.
30 Freeman JV, Higgins AY, Wang Y *et al*. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J. Am. Coll. Cardiol.* 2022; **79**: 1785–98.