Post-polypectomy bleeding and thromboembolism risks associated with warfarin vs direct oral anticoagulants

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AIM
To verify the validity of the endoscopy guidelines for patients taking warfarin or direct oral anticoagulants (DOAC).

METHODS
We collected data from 218 patients receiving oral anticoagulants (73 DOAC users, 145 warfarin users) and 218 patients not receiving any antithrombotics (age- and sex-matched controls) who underwent polypectomy. (1) We evaluated post-polypectomy bleeding (PPB) risk in patients...
receiving warfarin or DOAC compared with controls; (2) we assessed the risks of PPB and thromboembolism between three AC management methods: Discontinuing AC with heparin bridge (HPB) (endoscopy guideline recommendation), continuing AC, and discontinuing AC without HPB.

RESULTS

PPB rate was significantly higher in warfarin users and DOAC users compared with controls (13.7% and 13.7% vs 0.9%, P < 0.001), but was not significantly different between rivaroxaban (13.2%), dabigatran (11.1%), and apixaban (13.3%) users. Two thromboembolic events occurred in warfarin users, but none in DOAC users. Compared with the continuing anticoagulant group, the discontinuing anticoagulant with HPB group (guideline recommendation) had a higher PPB rate (10.8% vs 19.6%, P = 0.087). These findings were significantly evident in warfarin but not DOAC users. One thrombotic event occurred in the discontinuing anticoagulant without HPB group and the discontinuing anticoagulant without HPB group; none occurred in the continuing anticoagulant group.

CONCLUSION

PPB risk was similar between patients taking warfarin and DOAC. Thromboembolism was observed in warfarin users only. The guideline recommendations for HPB should be reconsidered.

Key words: High-risk endoscopic procedures; Novel oral anticoagulants; Endoscopic guideline validation; Post-procedure gastrointestinal bleeding

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Core tip: First, we found that anticoagulant (AC) users were at higher risk of post-polypectomy bleeding (PPB) than controls. Second, PPB risk was similar between warfarin users and direct oral anticoagulant users, whereas thromboembolism risk was observed only in warfarin users. Third, PPB risk was not significantly different between rivaroxaban, dabigatran, and apixaban users. Fourth, the strategy of discontinuing AC with heparin bridge as recommended in the endoscopy guidelines showed a higher bleeding rate than continuing AC alone and had one thrombotic event, thus indicating that heparin bridge increased bleeding and may not prevent thromboembolism.

INTRODUCTION

The number of oral anticoagulants (AC) used for prophylaxis or treatment of thromboembolic events is expected to increase as the population ages. Along with this, the number of colonoscopic polypectomies, the most common high-risk endoscopic procedure, is also expected to increase in patients receiving AC. Physicians are thus confronted with the issue of striking a balance between performing procedures with bleeding risk, such as polypectomy, and temporarily discontinuing AC agents to mitigate thromboembolic risk.

Among the AC agents commonly prescribed, warfarin requires careful and complex management because of its intricate pharmacodynamics and narrow therapeutic range, whereas direct oral anticoagulants (DOAC) offer easier management because of the rapid onset of anticoagulation and short half-lives. However, whether post-polypectomy bleeding (PPB) or thromboembolic risk differs between warfarin and DOAC users remains unknown.

Several endoscopy guidelines recommend discontinuing anticoagulation and short half-lives.
Patients underwent colonoscopic polypectomy between Aug 2010 and Dec 2016 and answered a questionnaire (n = 3120).

Cases
Receiving oral anticoagulants (n = 227)

Controls
Not receiving any antithrombotic drugs (n = 1981)

Review of endoscopic and clinical data for each patient

Cases (n = 218)
Receiving warfarin (n = 145) or DOAC (n = 73)
DOAC included: rivaroxaban (n = 38), dabigatran (n = 18), apixaban (n = 15) and edoxaban (n = 2)

Controls (n = 218)
Not receiving any antithrombotic drugs

Discontinuing AC with HPB group (n = 102)
Continuing AC group (n = 93)
Discontinuing AC without HPB group (n = 23)

Excluded (n = 9)
Clinical information not accurately collected (n = 6)
Underwent other endoscopic procedure simultaneously (n = 3)

Excluded (n = 1083)
Clinical information not accurately collected (n = 959)
Underwent other endoscopic procedure simultaneously (n = 93)
Lost to follow-up (n = 31)

Controls matched with cases for age and sex (1:1)

Figure 1 Patient selection and flow. AC: Anticoagulants; DOAC: Direct oral anticoagulants; HPB: Heparin bridge.

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was a retrospective study (approval number 2176).

Patient characteristics
Using the electronic database and prospectively collected questionnaire results, we assessed the following factors: height, weight, body mass index (BMI), alcohol, smoking, 14 comorbidities or past history (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, abnormal liver function, stroke, bleeding past history, chronic heart disease, vascular disease, acute coronary syndrome, pulmonary embolism, peripheral arterial disease, deep vein disease and advanced cancer), and medication [warfarin, rivaroxaban, dabigatran, apixaban, edoxaban, antiplatelet, and non-steroidal anti-inflammatory drugs (NSAIDs)]. We also evaluated laboratory data before colonoscopy [platelet count, prothrombin time-international normalized ratio (PT-INR), and creatinine clearance (Cr)] and calculated the HAS-BLED[16] and CHA2DS2-VASc2[17] scores. During hospitalization, data were collected on the following AC management factors: HPB use, HPB duration, drug continuation/discontinuation, and use of reversal agent (vitamin K).

Endoscopic factors
After full bowel preparation, polypectomies were done with or without local injection of saline using a high-resolution colonoscope (CF260AI or CF260AZI, Olympus Co., Tokyo, Japan), snare (SnareMaster, Olympus Co.), and electrosurgical device (ERBE ICC-350, Somo Technology Inc., Tokyo, Japan or ESG-100, Olympus Co.). After polypectomy, patients routinely underwent prophylactic clipping. Number of polyps and polyp size were evaluated from data in the endoscopic database. Advanced ade-
noma was defined as adenoma $\geq 1$ cm with villous components (tubulovillous or villous) or high-grade or severe dysplasia$^{[18]}$.

AC management and heparin bridge

American, European, and Asian guidelines$^{[6-8]}$ recommend that patients discontinue AC and be bridged with heparin before polypectomy, and to confirm the validity of this strategy, we classified patients during the peri-endoscopic period into three main AC management groups: (1) Discontinuing AC with HPB (as recommended by the guidelines); (2) continuing AC alone (i.e., without HPB) before endoscopy; and (3) discontinuing AC for $>24$ h without HPB before endoscopy. Which of these strategies was adopted was at the discretion of the treating physician.

For HPB, patients received prophylactic unfractionated heparin infusion intravenously (because low-molecular-weight heparin is not covered by Japan’s health care insurance system$^{[6,19]}$), with the exception of 1 patient who received low-molecular-weight heparin because of heparin-induced thrombocytopenia.

In our institution, we carry out anticoagulant management during high-risk endoscopy in accordance with the Japanese Endoscopy Guidelines$^{[8]}$; warfarin was stopped 3-5 d before endoscopy and DOAC was stopped 24-48 h after endoscopy. Heparin was administered after cessation of anticoagulants$^{[8]}$. INR value before polypectomy was set at $<1.5$ in warfarin users$^{[8]}$. In these users, heparin was continued until INR was optimal after polypectomy. Because the guidelines do not recommend HPB for DOAC users$^{[8]}$, some DOAC users continued heparin for one day and others did not use heparin after polypectomy. The HPB period included the entire period before and after polypectomy.

Clinical outcomes

The main outcomes of interest were PPB within 30 d of polypectomy. PPB was defined as massive, continuous, or frequent hematochezia after polypectomy$^{[20]}$. Not all patients underwent additional colonoscopy when PPB occurred, but those with unstable vital signs or in need of transfusion tended to undergo colonoscopy. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) bleeding scale as (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or periarticular, or intramuscular with compartment syndrome; and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells$^{[21]}$. In addition, we defined late PPB as bleeding occurring more than 24 h after polypectomy and all other cases as early PPB$^{[22]}$. We defined a thromboembolic event as the occurrence of acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism. We also evaluated mortality at 30 d after polypectomy. Date and cause of death were ascertained from the electronic medical records and death certificates.

Statistical analysis

Pearson’s chi-squared test or Fisher’s exact test was used for categorical data to assess the difference in risk factors between subjects. Continuous data were compared with Mann-Whitney U test. Risk factors were examined by univariate and multivariate analysis. Odds ratios (OR) and 95% confidence intervals (CI) were estimated.

First, we compared baseline characteristics and clinical outcomes between AC users and controls. Second, we compared baseline characteristics and clinical outcomes between the following groups: discontinuing AC with HPB and continuing AC group alone and between discontinuing AC with HPB group and discontinuing AC without HPB group. These comparisons were also evaluated for the subgroups of warfarin and DOAC users.

Third, to determine the risk factors for PPB, we conducted univariate and multivariate analysis. In multivariate analysis, we developed multivariate models adjusting for propensity score for each strategy. Although there are four different propensity score methods—matching, stratification, inverse probability treatment weighting, and covariates adjustment$^{[23,24]}$—we used propensity score as a covariate rather than perform a regression adjustment with all of the covariates (traditional covariate adjustment$^{[26]}$), because many covariates were associated with a small number of bleeding outcomes in this study and we did not want to lose the observations of patients as typically occurs in matching. Propensity score as a covariate method allows for a large number of baseline variables to be included in the regression model, which are not adequately adjusted for when there are insufficient numbers of outcomes$^{[23,24]}$. To estimate the propensity score, we employed a logistic regression model including potentially clinically important variables. Some of these were shown to differ ($P<0.10$) between groups. We evaluated the area under the receiver operating characteristic (ROC) curve for each propensity score in each group.

A $P$ value of $<0.05$ was considered statistically significant. All statistical analyses were conducted using STATA version 14 software (StataCorp, College Station, TX, United States).

RESULTS

Baseline characteristics and outcomes of AC users and controls

There were some significant differences in baseline characteristics between AC users and controls (Table 1). In terms of outcomes, there were 32 patients with PPB and only 2 patients with major bleeding, both of whom were warfarin users and received HPB. Four patients had early PPB (bleeding within 24 h) and 28 with late PPB: 9 cases at day 2, 9 cases at day 3, 6 cases at day
4, 1 case at day 5, 2 cases at day 6, and 1 case at day 8. The 4 patients with early PPB were all warfarin users. Compared with controls, there were a significantly higher rate among AC users of PPB (13.7% vs 9.9%, P < 0.001; Table 1). Two thromboembolic events occurred in AC users, but none in controls. Thromboembolicism occurred in 2 warfarin users and no DOAC users. No mortality events were noted in either group.

**Warfarin users vs DOAC users**

In the subgroup analysis of warfarin users, there were some significant differences in baseline characteristics with controls (Table 1). In terms of outcomes, warfarin users had a significantly higher rate of PPB (13.7% vs 9.9%, P < 0.001; Figure 2); a significantly increased PPB risk when adjusting for propensity score (adjusted OR = 18.6, P < 0.001; Table 2). In the subgroup analysis of DOAC users, there were also some significant differences in baseline characteristics with controls (Table 1). As for outcomes, DOAC users had a significantly higher rate of PPB (13.8% vs 9.9%, P < 0.001; Table 2); significantly increased PPB risk when adjusting for propensity score (adjusted OR = 17.8, P = 0.001; Figure 2); a significantly increased PPB risk when adjusting for propensity score (adjusted OR = 17.8, P = 0.001; Figure 2). Two thromboembolic events occurred in AC users, but none in controls. Thromboembolicism occurred in 2 warfarin users and no DOAC users. No mortality events were noted in either group.

### Table 1 Baseline characteristics of oral anticoagulant users, warfarin users, direct oral anticoagulants users, and controls not taking any antithrombotic drugs (n = 436) n (%)

| Factors | Controls (n = 218) | AC users (n = 218) | P value Control vs AC | Warfarin users (n = 145) | P value Control vs warfarin users | DOAC users (n = 73) | P value Control vs DOAC users |
|---------|-------------------|-------------------|-----------------------|--------------------------|----------------------------------|---------------------|-----------------------------|
| Age ≥ 75 yr | 104 (47.1) | 113 (51.8) | 0.389 | 79 (54.5) | 0.206 | 34 (46.6) | 0.867 |
| Male | 157 (72.0) | 157 (72.0) | 1.000 | 103 (71.0) | 0.839 | 54 (74.0) | 0.746 |
| BMI ≥ 25 | 54 (24.8) | 69 (31.7) | 0.110 | 44 (30.3) | 0.241 | 25 (34.2) | 0.115 |
| Drinker | 119 (54.6) | 131 (62.1) | 0.115 | 77 (55.4) | 0.881 | 54 (75.0) | 0.002 |
| Smoker | 36 (16.5) | 32 (14.8) | 0.626 | 21 (14.6) | 0.622 | 11 (15.3) | 0.805 |
| Laboratory data | | | | | | | |
| Platelet < 10 × 10^12 μL | 6 (2.8) | 5 (2.3) | 1.000 | 3 (2.1) | 1.000 | 2.7 (2.7) | 1.000 |
| Ccr < 30 mL/min | 9 (4.1) | 24 (11.0) | 0.007 | 20 (13.8) | 0.001 | 5 (4.58) | 0.743 |
| Comorbidities | | | | | | | |
| Diabetes mellitus | 45 (20.6) | 52 (23.9) | 0.420 | 39 (26.9) | 0.166 | 13 (17.8) | 0.600 |
| Hypertension | 121 (55.4) | 148 (67.9) | 0.008 | 94 (64.8) | 0.077 | 54 (74.0) | 0.005 |
| Dyslipidemia | 74 (33.9) | 102 (46.8) | 0.006 | 67 (46.2) | 0.019 | 35 (48.0) | 0.037 |
| Chronic kidney disease | 49 (22.5) | 37 (17.0) | 0.149 | 32 (22.1) | 0.927 | 5 (6.9) | 0.003 |
| Abnormal liver function | 15 (6.9) | 8 (3.7) | 0.134 | 3 (2.1) | 0.047 | 5 (6.9) | 0.993 |
| Stroke | 10 (4.6) | 47 (21.6) | 0.001 | 29 (20.0) | 0.001 | 18 (24.7) | 0.001 |
| Bleeding past history | 21 (9.6) | 13 (6.0) | 0.153 | 10 (6.9) | 0.361 | 3 (4.1) | 0.217 |
| Chronic heart failure | 1 (0.5) | 56 (25.7) | 0.001 | 46 (31.7) | 0.001 | 10 (13.7) | 0.001 |
| Vascular disease | 6 (2.8) | 56 (25.7) | 0.001 | 49 (33.8) | 0.001 | 7 (9.6) | 0.014 |
| Acute coronary syndrome | 6 (2.8) | 34 (15.6) | 0.001 | 28 (19.3) | 0.001 | 6 (8.2) | 0.042 |
| Pulmonary embolism | 0 (0.0) | 7 (3.2) | 0.008 | 6 (4.1) | 0.004 | 1 (1.4) | 0.251 |
| Peripheral arterial disease | 0 (0.0) | 7 (3.2) | 0.008 | 6 (4.1) | 0.004 | 1 (1.4) | 0.251 |
| Deep vein thrombosis | 0 (0.0) | 14 (6.4) | 0.001 | 14 (9.7) | 0.001 | 0 NA | |
| Advanced carcinoma | 7 (3.2) | 33 (15.1) | 0.001 | 21 (14.5) | 0.001 | 12 (16.4) | 0.001 |
| Medications | | | | | | | |
| Antiplatelet | 0 (0.0) | 53 (24.3) | 0.001 | 43 (30.0) | 0.001 | 10 (13.7) | 0.001 |
| Low-dose aspirin | 0 (0.0) | 40 (18.4) | 0.001 | 33 (22.8) | 0.001 | 7 (9.6) | 0.001 |
| Thienopyridine¹ | 0 (0.0) | 5 (2.3) | 0.025 | 5 (3.5) | 0.006 | 0 (0.0) | |
| Other antiplatelets² | 0 (0.0) | 11 (5.1) | 0.001 | 8 (5.5) | 0.001 | 3 (4.1) | 0.003 |
| NSAIDs | 21 (9.6) | 7 (3.2) | 0.006 | 3 (2.1) | 0.004 | 4 (5.5) | 0.341 |
| Endoscopic factors | | | | | | | |
| Number of polyps ≤ 5 | 2.0 ± 1.4 | 8.3 ± 5.3 | 0.019 | 2.4 ± 1.8 | 0.063 | 2.5 ± 1.8 | 0.041 |
| Number of polyps ≥ 5 | 13 (6.0) | 28 (12.8) | 0.014 | 17 (11.7) | 0.078 | 11 (15.1) | 0.014 |
| Polyp size | 6.0 ± 3.3 | 6.3 ± 3.4 | < 0.001 | 8.7 ± 5.9 | < 0.001 | 7.4 ± 3.7 | 0.001 |
| Polyp size ≥ 10 mm | 28 (12.8) | 69 (31.7) | < 0.001 | 47 (32.4) | < 0.001 | 22 (30.1) | 0.001 |
| Advanced adenoma³ | 27 (12.4) | 64 (29.4) | < 0.001 | 43 (29.7) | < 0.001 | 21 (28.8) | 0.001 |

¹Thienopyridine includes ticlopidine, clopidogrel, and prasugrel; ²Other antiplatelets are antiplatelets other than low-dose aspirin and thienopyridine; ³Advanced adenoma is adenoma ≥ 1 cm with villous components (tubulovillous or villous) or high-grade or severe dysplasia. Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD. Bold type indicates statistical significance (P < 0.05). AC: Anticoagulant; DOAC: Direct oral anticoagulants; BMI: Body mass index; Ccr: Creatinine clearance; NSAIDs: Non-steroidal anti-inflammatory drugs.
Propensity score-adjusted OR = 2.2 (95%CI: 1.1-4.3) for warfarin users vs controls (P = 0.020; Figure 3A); increased PPB risk on univariate analysis (OR = 7.2, P = 0.033; Table 3). In the DOAC subgroups, there were no significant differences in PPB risk between the two subgroups (Table 3).

Association of rate of PPB with HPB duration and INR value at endoscopy
The rate of PPB increased significantly with longer duration of HPB (P = 0.015 for trend; Figure 4). This trend was also found in warfarin and DOAC users (Figure 4). Rate of PPB was 18.7% for INR < 1.5, 0% for INR 1.5-1.9, 25% for INR 2.0-2.4, and 0% for INR > 2.5. INR value at pre-endoscopy did not predict PPB (P = 0.431 for trend; Supplementary Figure 1).

DISCUSSION
The four main findings of the study are as follows: (1) AC users were at higher risk of PPB than controls; (2) PPB risk was similar between warfarin users and DOAC users, whereas thromboembolism risk was observed only in warfarin users; (3) PPB risk was not significantly different
between rivaroxaban, dabigatran, and apixaban users; and (4) the recommended strategy of discontinuing AC with HPB showed a higher bleeding rate than continuing AC alone and had one thrombotic event, indicating that HPB increased bleeding and may not prevent thromboembolism. These findings were significantly evident in warfarin users compared with DOAC users.

In agreement with past studies, our AC users had a significantly higher OR for PPB than did controls (adjusted OR = 18.9). Witt et al. reported that PPB occurred more often in AC users than non-AC users (adjusted OR = 11.6). Hui et al. demonstrated that warfarin use was an independent risk factor for PPB (adjusted OR = 13.4). The ORs in these studies were lower than ours because their control subjects included antiplatelet users.

We revealed for the first time in this study that PPB risk was similar between warfarin and DOAC users compared with controls. A meta-analysis study indicated a higher risk of non-procedural-related bleeding in DOAC users than in warfarin users. Thus, bleeding risk might be different between procedure-related and non-procedure-related bleeding. Only limited data are available on differences in post-endoscopic bleeding between DOAC and warfarin users. In this study, we found that 14% of DOAC and warfarin users had PPB. In agreement with this, Nagata et al. showed that 14% of DOAC users had PPB and 16.9% of warfarin users had PPB (P = 0.324). However, post-polypectomy-related bleeding differ according to site of the bleed in the upper or lower GI tract, because upper GI polypectomy-related bleeding was higher in warfarin users than in DOAC users (P = 0.06).

Several endoscopy guidelines recommend that AC be discontinued with HPB. However, in our study, following

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**Figure 3** Post-polypectomy bleeding according to the three main anticoagulants management strategies in anticoagulants (A), warfarin (B), and direct oral anticoagulants (C) users. For the 218 patients, 102 patients (46.8%) in the discontinuing anticoagulants with heparin bridge group, 93 (42.7%) in the continuing anticoagulants group, and 23 (10.6%) in the discontinuing anticoagulants without heparin bridge group. AC: Anticoagulants; DOAC: Direct oral anticoagulants; HPB: Heparin bridge.
this guideline strategy showed a higher bleeding risk and longer hospital stay compared with the continuing AC strategy, and one thrombotic event occurred with the guideline strategy and none in the continuing AC strategy. These findings suggest that continuing oral AC might be acceptable for polypectomy.

Consistent with our results, a meta-analysis[30] showed that HPB was associated with a higher rate of PPB and did not prevent thromboembolism. A randomized study[13] found that post-procedural bleeding risk was higher in patients with HPB than in those without it, and thromboembolic risk was similar in both groups. Taken together, the evidence suggests that the recommendation of several endoscopic guidelines[6-8] should be re-evaluated.

It is not clear why following the guideline strategy was associated with increased PPB risk in warfarin users but not DOAC users. One possible explanation is that in warfarin users, it takes several days for the anticoagulant effect to be sufficient, whereas onset is rapid with DOAC and therapeutic anticoagulation is achieved in a few hours[31]. The criterion for discontinuing heparin in warfarin users is that INR reaches the effective range, but the time to reach this range varies among patients. Therefore, heparin may need to be used for a long time after the procedure; the time is much shorter in DOAC users. Also, simultaneously administering warfarin and heparin (double anticoagulation effect) can increase bleeding risk. From these considerations, GI bleeding risk is high when HPB is performed in warfarin users compared with DOAC users. These prior findings, together with ours here, suggest that warfarin should be switched to DOAC before high-risk endoscopic procedures are performed.

### Table 3

| AC management during peri-endoscopic period | Crude OR (95%CI) | P value | Propensity score-adjusted OR (95%CI) | P value |
|-------------------------------------------|------------------|---------|-------------------------------------|---------|
| AC users                                  |                  |         |                                     |         |
| Discontinuing AC with HPB vs continuing AC | 2.0 (0.9-4.6)    | 0.091   | 2.2 (0.9-5.2)                       | 0.069   |
| Discontinuing AC with HPB vs discontinuing AC without HPB | 7.7 (1.3-Inf) | 0.023 | NA | NA |
| Warfarin users                            |                  |         |                                     |         |
| Discontinuing warfarin with HPB vs continuing warfarin | 5.7 (1.3-25.8) | 0.024 | 4.7 (1.0-22.1) | 0.049 |
| Discontinuing warfarin with HPB vs discontinuing warfarin without HPB | 7.2 (1.1-Inf) | 0.033 | NA | NA |
| DOAC users                                |                  |         |                                     |         |
| Discontinuing DOAC with HPB vs continuing DOAC | 0.6 (0.1-3.2) | 0.567 | 0.7 (0.1-4.5) | 0.664 |
| Discontinuing DOAC with HPB vs discontinuing DOAC without HPB | 0.5 (0.4-Inf) | 1.000 | NA | NA |

1Propensity score estimations. Values in parentheses are percentages. Values presented with a plus/minus sign are means ± SD; bold type indicates statistical significance (P < 0.05). Continuing AC group vs standard group: Logistic regression model included 8 factors that are potentially clinically important variables; area under the ROC curve for propensity scores for the continuing AC group was 0.71 (95%CI: 0.63-0.79); standard group vs continuing warfarin group: Logistic regression model included 6 factors that are potentially clinically important variables; area under the ROC curve for propensity scores for the continuing warfarin group was 0.63 (95%CI: 0.53-0.73); standard group vs continuing DOAC group: Logistic regression model included 6 factors that are potentially clinically important variables; area under the ROC curve for propensity scores for the continuing DOAC group was 0.90 (95%CI: 0.82-0.98). NA: Not applicable; AC: Anticoagulants; CI: Confidential interval; DOAC: Direct oral anticoagulants; HPB: Heparin bridge; Inf: Infinity; OR: Odds ratio.

### Figure 4

Association of post-polypectomy bleeding rate with duration of heparin bridge in anticoagulants, warfarin, and direct oral anticoagulants users. AC: Anticoagulants; WF: Warfarin; DOAC: Direct oral anticoagulants; HPB: Heparin bridge; PPB: Post-polypectomy bleeding.

*P* = 0.015 for trend in AC users

*P* = 0.076 for trend in WF users

*P* = 0.092 for trend in DOAC users
One of the strengths of our study was the analysis of detailed clinical and endoscopic data that was collected and that we could adjust for propensity score by including these factors in the multivariate models. Another was that we identified a difference in clinical outcomes between the three main AC management strategies investigated. We also recognize limitations. First, this was a retrospective study conducted at a single site. Second, the AC users were heterogeneous and included those with atrial fibrillation, valvular disease, or with low or high thromboembolic risk. Third, we have no data on subcutaneous heparin because intravenous heparin is used in Japan. However, a previous study reported a similar incidence of major bleeding between patients treated with subcutaneous unfractionated heparin and those treated with intravenous unfractionated heparin (OR 0.91).

In conclusion, patients receiving oral AC had higher risks of bleeding after colonoscopic polypectomy compared with patients not receiving any antithrombotics. PPB risk was similar between warfarin and DOAC users, whereas thromboembolism risk was observed in warfarin users only. HPB increased bleeding risk, and may not prevent thromboembolism and therefore the current guideline recommendation should be re-considered. Continuing oral AC may be acceptable for polypectomy.

ARTICLE HIGHLIGHTS

Research background
The number of oral anticoagulants (AC) used increases as the population ages, and the number of colonoscopic polypectomies is expected to increase in patients receiving AC.

Research motivation
Whether post-polypectomy bleeding (PPB) or thromboembolic risk differs between warfarin and direct oral anticoagulant (DOAC) users remains unknown.

Research objectives
We evaluated PPB risk in patients receiving warfarin or DOAC compared with patients not receiving any antithrombosis (controls). We also assessed the risks of PPB and thromboembolism between the three AC management methods mentioned above, discontinuing AC with heparin bridge (guideline recommendation), continuing AC, and discontinuing AC without heparin bridge.

Research methods
We conducted a retrospective cohort study and collected data from 218 patients receiving oral anticoagulants (73 DOAC users, 145 warfarin users) and 218 patients not receiving any antithrombotics (age- and sex-matched controls) who underwent polypectomy.

Research results
PPB rate was significantly higher in both warfarin users and DOAC users compared with controls. Two thromboembolic events occurred in warfarin users, but none in DOAC users. Compared with the continuing anticoagulant group, the discontinuing anticoagulant with heparin bridge group (guideline recommendation) had a higher PPB rate. One thrombotic event occurred in the discontinuing anticoagulant with heparin bridge group and the discontinuing anticoagulant without heparin bridge group; none occurred in the continuing anticoagulant group.

Research conclusions
Patients receiving oral anticoagulant had higher risks of bleeding after colonoscopic polypectomy compared with patients not receiving any antithrombotics. PPB risk was similar between warfarin and DOAC users, whereas thromboembolism risk was observed in warfarin users only. Heparin bridge increased bleeding risk, and may not prevent thromboembolism.

Research perspectives
The current guideline recommendation for heparin bridge should be re-considered, and continuing oral anticoagulant may be acceptable for polypectomy.

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