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Continuous Anticoagulation and Cold Snare Polypectomy Versus Heparin Bridging and Hot Snare Polypectomy in Patients on Anticoagulants With Subcentimeter Polyps

A Randomized Controlled Trial

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Background: Management of anticoagulants for patients undergoing polypectomy is still controversial. Cold snare polypectomy (CSP) is reported to cause less bleeding than hot snare polypectomy (HSP).

Objective: To compare outcomes between continuous administration of anticoagulants (CA) with CSP (CA+CSP) and periprocedural heparin bridging (HB) with HSP (HB+HSP) for subcentimeter colorectal polyps.

Design: Multicenter, parallel, noninferiority randomized controlled trial. (University Hospital Medical Information Network Clinical Trials Registry: UMIN000019355)

Setting: 30 Japanese institutions.

Patients: Patients receiving anticoagulant therapy (warfarin or direct oral anticoagulants) who had at least 1 nonpedunculated subcentimeter colorectal polyp.

Intervention: Patients were randomly assigned to undergo HB+HSP or CA+CSP and followed up 28 days after polypectomy.

Measurements: The primary end point was incidence of polypectomy-related major bleeding (based on the incidence of poorly controlled intraprocedural bleeding or postpolypectomy bleeding requiring endoscopic hemostasis). The prespecified inferiority margin was −5% (CA+CBP vs. HB+HSP).

Results: A total of 184 patients were enrolled: 90 in the HB+HSP group, 92 in the CA+CSP group, and 2 who declined to participate after enrollment. The incidence of polypectomy-related major bleeding in the HB+HSP and CA+CSP groups was 12.0% (95% CI, 5.0% to 19.1%) and 4.7% (CI, 0.2% to 9.2%), respectively. The intergroup difference for the primary end point was +7.3% (CI, −1.0% to 15.7%), with a 0.4% lower limit of 2-sided 90% CI, demonstrating the noninferiority of CA+CSP. The mean procedure time for each polyp and the hospitalization period were longer in the HB+HSP than in the CA+CSP group.

Limitation: An open-label trial assessing 2 factors (anticoagulation approach and polypectomy procedure type) simultaneously.

Conclusion: Patients having CA+CSP for subcentimeter colorectal polyps who were receiving oral anticoagulants did not have an increased incidence of polypectomy-related major bleeding, and procedure time and hospitalization were shorter than in those having HB+HSP.

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* For members of the Madowazu Study Group, see **Appendix 1** (available at Annals.org).

Polypectomy reduces the morbidity and mortality associated with colorectal cancer (1–5). As the population ages and indications for anticoagulation therapy expand (6), the number of patients receiving anticoagulants is increasing (7, 8). Anticoagulants confer an increased risk for hemorrhage, but their withdrawal also poses risks for thromboembolic sequelae (9). Guidelines on peripolypectomy management of anticoagulants vary greatly, and the current updated guidelines do not recommend heparin bridging (HB) for all patients; however, direct comparison of HB with continuous administration of oral anticoagulants (CA) has provided little evidence (10–14).

Cold snare polypectomy (CSP), which does not involve electrocautery, is reported to be safe and effective and is recommended by the European Society of Gastrointestinal Endoscopy as standard care for subcentimeter polyps (15–17). A randomized controlled trial (RCT) reported that CSP may decrease delayed bleeding in persons receiving warfarin (18). However, the RCT did not compare a new strategy (CSP with CA [CA+CSP]) with a conventional one (hot snare polypectomy [HSP] with HB [HB+HSP]) (19) and did not include patients receiving direct oral anticoagulants (DOACs), although the use of DOACs is increasing (20).

Cold snare polypectomy with CA may be performed safely, without the complications of HB, while theoretically

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maintaining an anticoagulant effect. Therefore, CA+CSP might be a standard approach to removing subcentimeter polyps in patients receiving anticoagulants if the incidence of severe adverse events is noninferior to that of HB+HSP, the conventional strategy. Therefore, we conducted a multicenter RCT to investigate the noninferiority of CA+CSP versus HB+HSP for treating subcentimeter colorectal polyps.

METHODS

Design Overview

The study was designed as an open-label, parallel (1:1), multicenter RCT. The study protocol (**Supplement**, available at Annals.org) was developed by the steering committee and approved by the research ethics committee of the participating clinical centers (Osaka International Cancer Institute, 31 March 2016). The trial recruited patients from 29 June 2016 to 27 December 2017, and follow-up was completed on 26 April 2018. No major changes to study procedures or outcomes occurred after the trial began. The study followed the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement (21) and was registered on 1 June 2016 in the University Hospital Medical Information Network Clinical Trials Registry as UMIN000022461. All eligible patients provided written informed consent to participate. An independent efficacy and safety committee monitored patient safety, adverse events, and the trial's progress.

Setting and Participants

The study was conducted at 30 Japanese academic or tertiary institutions (Madowazu Study Group). Patients were eligible to participate in the trial if they were aged 20 to 80 years, had an Eastern Cooperative Oncology Group Performance Status score of 1 or lower, were receiving anticoagulation therapy with warfarin or DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban), had preserved organ function (platelet count $\geq 100 \times 10^9$/L; creatinine concentration ≤176.8 μmol/L [2.0 mg/dL]; and, for patients receiving DOACs, prothrombin time [PT] ≥40%), and had at least 1 subcentimeter nonpedunculated polyp detected during colonoscopy in the past 3.5 years. Patients receiving warfarin were required to have a PT international normalized ratio (PT-INR) in the therapeutic range (1.5 to 3.0). Patients were not eligible if they had lesions that were 10 mm or larger, lesions suspected to be cancerous, pedunculated polyps, or depressed polyps; were receiving antiplatelet drugs and could not discontinue treatment according to the Japanese guideline (19); or had other conditions (**Appendix 2**, available at Annals.org). Recruitment was not regulated, and potential participants were identified mainly by the attending physician or clinical research coordinator. Eligibility and informed consent were confirmed by the study investigators. An ineligible polyp detected during colonoscopy and treated at the colonoscopist's discretion was considered a protocol deviation.

Randomization and Intervention

Randomization was performed by using a computer-generated system at Medical Research Support (Kyoto, Japan) with a program available on the Web. On the basis of allocation adjustment factors among the institutions, the known number of polyps (≤4 or ≥5), and anticoagulant therapy (warfarin or DOACs), participants were randomly assigned (1:1) to receive conventional treatment (HB+HSP group) or investigational therapy (CA+CSP group) according to a minimization method, without the use of blocks. Then, the allocated interventions were displayed so that the sequence was concealed to the colonoscopists until the participants were assigned. Neither the colonoscopists nor the participants were blinded to the allocated groups.

Polypectomy was performed on an inpatient basis. The plan for anticoagulant management is shown in the **Appendix Figure** (available at Annals.org) and described in **Appendix 3** (available at Annals.org); details regarding colonoscopy and polypectomy are given in **Appendix 4** (available at Annals.org).

After polypectomy, the endoscopist observed bleeding from the mucosal defect for at least 30 seconds. Hemostasis clips were applied immediately if blood was spurting or if bleeding did not slow. Cautery was performed with an electric current if hemostasis could not be achieved with clips. If hemostasis could not be achieved endoscopically, interventional radiology or surgery was recommended. Prophylactic hemostasis was not standardized for either group.

Outcomes and Follow-up

The primary end point was the incidence of polypectomy-related major bleeding, defined as poorly controlled intraprocedural bleeding requiring transfusion, surgery, or interventional radiology, or postpolypectomy bleeding requiring endoscopic hemostasis within 28 days after polypectomy. Postpolypectomy bleeding requiring endoscopic hemostasis was defined as postprocedural bleeding necessitating emergency endoscopy. Emergency endoscopy was performed for bleeding accompanied by 2 or more consecutive episodes of hematochezia or melena that did not show signs of improvement, for changes in vital signs (diastolic pressure <100 mm Hg and heart rate >90 beats/min), or for a decrease in hemoglobin level of 20 g/L or greater; endoscopic hemostasis was performed for endoscopic findings of gastrointestinal bleeding classified as Forrest Ia, Ib, or IIa (22).

Secondary end points were mean procedure time; incidence of intraprocedural bleeding requiring hemostasis immediately after polyp excision; incidence of postpolypectomy hematochezia or melena not requiring emergency endoscopic hemostasis; mean days of hospitalization; mean number of colonoscopic examinations until removal of all detected polyps; and adverse events, including data obtained from a patient survey 28 days after polypectomy. We also examined the characteristics of postpolypectomy bleeding cases.

All events during hospitalization were assessed by hospital staff (nurses and colonoscopists) (**Appendix 5**,

available at Annals.org). Patients scheduled an appointment for 14 days after polypectomy, and the presence of postdischarge adverse events was assessed by a nonblinded outpatient physician. At the outpatient visit, patients completed a survey form inquiring about whether they had adverse events but not severity or causality. Patients also were given a survey comprising a checklist of adverse events (hematochezia, abdominal pain, bloating, and diarrhea) that might occur within 28 days after treatment; the participants then mailed the completed surveys to the investigators (23).

Statistical Analysis

On the basis of previous reports about warfarin and HB (few data on DOACs were available when we conceived this trial) (18, 24), we hypothesized that the incidence of severe bleeding would be 10% in the HB+HSP group and 3% in the CA+CSP group. The noninferiority margin between the 2 groups was set to −5%, which is the maximum tolerable inferiority of CA+CSP to HB+HSP, based on our discussion about the clinical relevance of the new strategy. With $\alpha = 0.05$ (1-sided) and $\beta = 0.10$ (normal approximation), 72 participants were required in both groups. The target enrollment was set at 90 patients per group to account for a withdrawal and ineligibility rate of 20%.

Intention-to-treat analysis was defined as analysis of all randomly assigned participants. The full analysis set (FAS) was defined as all participants who were randomly assigned and had polypectomy, after excluding those who violated eligibility or exclusion criteria, did not receive the study treatment (had treatment other than the one assigned), or did not have postrandomization data. The per protocol set (PPS) was defined as all participants who were randomly assigned and had polypectomy, without important deviations from the protocol.

To test the noninferiority of the primary end point, we used the lower limit of the 2-sided 90% CI (Wald) as a boundary, which corresponds to a 1-sided 95% lower confidence limit. If it exceeded −5% (if the difference in the proportion was the difference obtained by subtracting the bleeding rate in the CA+CSP vs. HB+HSP groups in the FAS), we would declare CA+CSP to be noninferior to HB+HSP in the setting of this study.

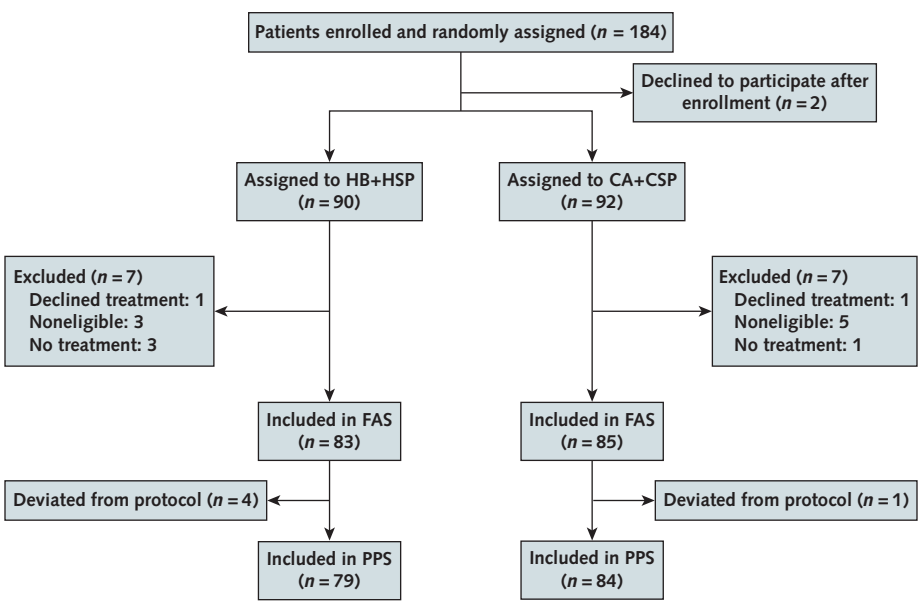
Secondary outcomes, including adverse events, also were evaluated in the FAS, and the PPS was used for sensitivity analysis for the primary outcome. We calculated 95% CIs for all outcomes in both groups, as well as the differences between the groups. For secondary outcomes, we used Fisher exact and *t* tests for categorical and continuous variables, respectively. Missing data were excluded from each analysis, and the number of missing data is shown in each table.

We did not have stopping guidelines and did not perform an interim analysis. Data analysis was conducted by using SAS, version 9.4 (SAS Institute). All *P* values were 2-tailed, and $P < 0.050$ was defined as statistically significant. More details are presented in Appendix 6 (available at Annals.org).

Role of the Funding Source

The Japanese Gastroenterological Association had no role in the design or conduct of the trial, the analysis or interpretation of the results, or the decision to submit the manuscript for publication.

Figure 1. Patient recruitment and selection.



CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; FAS = full analysis set; HB = heparin bridging; HSP = hot snare polypectomy; PPS = per protocol set.

Table 1. Baseline Characteristics of the Full Analysis Set

Characteristic	Study Group	
	HB+HSP (*n* = 83)	CA+CSP (*n* = 85)
Patients, *n (%)*		
Male	68 (82)	76 (89)
Female	15 (18)	9 (11)
Median age (IQR), *y*	73 (68–76)	73 (70–76)
Mean BMI (SD), *kg/m²*	23.7 (3.7)	24.8 (3.1)
Anticoagulant use		
Warfarin, *n (%)*	25 (30)	30 (35)
Median dose (IQR), *mg/d*	2.75 (2.5–3.5)	3 (2.4–4.0)
DOACs, *n (%)*	58 (70)	55 (65)
Dabigatran	8 (14)	5 (9)
Rivaroxaban	29 (50)	20 (36)
Apixaban	13 (22)	20 (36)
Edoxaban	8 (14)	10 (18)
Antiplatelet use, *n (%)*		
Aspirin	5 (6)	8 (9)
Clopidogrel	1 (1)	2 (2)
Cilostazol	1 (1)	3 (3)
Other	1 (1)	1 (1)
Comorbidity		
Median Charlson Comorbidity Index score (range)	0 (0–4)	0 (0–4)
Distribution, *n (%)*		
0	69 (83)	75 (88)
1	9 (11)	4 (5)
2	4 (5)	3 (4)
3	0 (0)	2 (2)
4	1 (1)	1 (1)
Median CHA_2DS_2-VASc score (range)*	3 (0–6)	3 (0–6)
Distribution, *n (%)*		
0	1 (1)	2 (2)
1	14 (17)	12 (14)
2	24 (29)	18 (21)
3	23 (28)	23 (27)
4	12 (14)	16 (19)
5	4 (5)	9 (11)
6	5 (6)	5 (6)
Mean laboratory values (SD)		
Hemoglobin level, *g/L*	137 (18)	140 (16)
Platelet count, × 10^9 *cells/L*	200 (61)	196 (55)
Creatinine level		
μmol/L	77.8	82.2
mg/dL	0.88 (0.19)	0.93 (0.21)
PT, %	64.4 (26.0)	60.6 (25.0)
PT-INR ratio		
Patients receiving warfarin	1.86 (0.46)	1.98 (0.45)
Patients receiving DOACs	1.21 (0.21)	1.19 (0.16)
aPTT, *s*		
Patients receiving warfarin	38.9 (8.0)	39.7 (8.2)†
Patients receiving DOACs	37.7 (9.1)	38.1 (10.7)

aPTT = activated partial thromboplastin time; BMI = body mass index; CA = continuous administration of oral anticoagulants; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, Stroke, Vascular disease, Sex female; CSP = cold snare polypectomy; DOACs = direct oral anticoagulants; HB = heparin bridging; HSP = hot snare polypectomy; INR = international normalized ratio; IQR = interquartile range; PT = prothrombin time.
* Reference 31.
† Data missing for 1 patient.

RESULTS

Recruitment and Participant Flow

Between June 2016 and December 2017, a total of 184 patients undergoing colonoscopy enrolled in the study. Median time from written informed consent and confirmation of eligibility to enrollment and randomization was 0 days (interquartile range, 0 to 0 days). Information for 2 patients was excluded from the database because they decided not to take part in the study after being enrolled. Thus, 90 patients were assigned to the

HB+HSP group and 92 to the CA+CSP group. After treatment allocation, 1 patient in both groups retracted their consent and declined to participate. Three patients in the HB+HSP group and 5 in the CA+CSP group were excluded because they were found to be ineligible: 2 patients in the HB+HSP group and 3 in the CA+CSP group had polyps 10 mm or larger or a lesion suspicious for invasive cancer, 1 patient in the HB+HSP group had been enrolled in the study previously, and 2 patients in the CA+CSP group were not receiving anticoagulant therapy. Three patients in the HB+HSP group and 1 patient in the CA+CSP group did not have colonoscopy because their underlying diseases had been aggravated between study enrollment and polypectomy. As a consequence, 83 patients in the HB+HSP group and 85 in the CA+CSP group were included in the FAS (Figure 1). Four patients in the HB+HSP group and 1 patient in the CA+CSP group did not have all detected polyps removed because there were too many to extract during 1 colonoscopy. Therefore, these cases were considered protocol deviations and excluded from the PPS analysis.

Baseline Data and Anticoagulant Management

Although no outcomes data were missing, some laboratory values were absent for a few patients and were excluded (Tables 1 to 3 and Appendix Table 1, available at Annals.org). Baseline data were analyzed between groups and were not significantly different (Table 1). The most common reason for anticoagulant use was atrial fibrillation (Appendix Table 2, available at Annals.org). The PT-INR was within therapeutic range among patients receiving warfarin and within normal range for those receiving DOACs. Periprocedural anticoagulant therapy was managed mostly according to protocol (Appendix Table 1). The PT-INR among patients in the HB+HSP group who were receiving warfarin returned to normal range and was significantly lower than that of the CA+CSP group on the morning of polypectomy. The PT-INR and activated partial thromboplastin time were almost similar between the morning after and the morning of polypectomy in both groups.

Outcomes and Estimation

A total of 631 lesions were detected, and 611 eligible lesions were removed from 168 patients. Four lesions larger than 10 mm and 1 lesion suspected to be cancerous were detected and removed outside of protocol. Although the median number of detected and eligible lesions, as well as the size and morphology of the removed lesions, did not differ between the 2 groups, polyps were distributed in the right colon more frequently in the CA+CSP than in the HB+HSP group. Prophylactic hemostasis was performed more often in the HB+HSP than in the CA+CSP group (Table 2).

The incidence of polypectomy-related major bleeding (primary end point) was 4.7% (95% CI, 0.2% to 9.2%) in the CA+CSP group and 12.0% (CI, 5.0% to 19.1%) in the HB+HSP group. The intergroup difference for the incidence of polypectomy-related major bleeding was 7.3% (CI, −1.0% to 15.7%), the lower limit of the 2-sided 90% CI was 0.4%, and the risk ratio was 2.56 (CI, 0.84 to 7.84) (Figure 2 and Table 3). In the subgroup analysis, noninferiority of the primary end point also was observed both in patients receiving warfarin and those taking DOACs. Poorly controlled intraprocedural bleeding did not occur in either the CA+CSP or HB+HSP group, and all polypectomy-related major bleeding cases were post-

Table 2. Procedure-Related Factors

Factor	Study Group		*P* Value
	HB+HSP (*n* = 83)	CA+CSP (*n* = 85)	
Lesions			
Median detected (IQR), *n*	3 (2–5)	3 (2–5)	0.26
Median targeted (IQR), *n*	3 (2–4)	3 (2–5)	0.144
Median removed (IQR), *n*	3 (1–4)	3 (2–5)	0.36
Total removed, *n*	286	325	
Median size (range), *mm*	5 (3–6)	5 (3–6)	0.76
Diminutive (1–5 mm), *n (%)*	206 (72)	223 (69)	0.38
Small (6–9 mm), *n (%)*	80 (28)	102 (31)	
Location, *n (%)*			0.018
Right-sided colon	169 (59)	222 (68)	
Left-sided colon and rectum	117 (41)	103 (32)	
Morphologic characteristics, *n (%)*			0.55
Polypoid	187 (65)	204 (63)	
Nonpolypoid	99 (35)	121 (37)	
Pathologic characteristics, *n (%)*			0.008
Adenoma*	246 (86)	302 (93)	
Invasive cancer	0 (0)	0 (0)	
Serrated polyp/nonneoplastic	35 (12)	22 (7)	
Not retrieved, *n (%)*	5 (2)	1 (0.3)	
Submucosal injection, *n/N (%)*	126/284 (44)†	0/0 (0)	
Prophylactic hemostasis, *n/N (%)*	38/286 (13)	6/325 (2)	<0.001

CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; HB = heparin bridging; HSP = hot snare polypectomy; IQR = interquartile range.
* Including intramucosal carcinoma.
† Data are missing for 1 patient.

Table 3. Study End Points

End Point	Study Group		Risk Difference (95% CI), *percentage points*
	HB+HSP	CA+CSP	
Primary, *n/N (% [95% CI])*			
Polypectomy-related major bleeding	10/83 (12.0 [5.0 to 19.1])	4/85 (4.7 [0.2 to 9.2])	7.3 (−1.0 to 15.7)
Poorly controlled intraprocedural bleeding	0	0	–
Postpolypectomy bleeding requiring endoscopic hemostasis	10/83 (12.0 [5.0 to 19.1])	4/85 (4.7 [0.2 to 9.2])	7.3 (−1.0 to 15.7)
Patients receiving warfarin	3/25 (12.0 [0 to 24.7])	0/30 (0 [0 to 11.6])	12.0 (−0.7 to 24.7)
Patients receiving DOACs	7/58 (12.1 [3.7 to 20.5])	4/55 (7.3 [0.4 to 14.1])	4.8 (−6.0 to 15.6)
			***P* Value**
Secondary			
Mean procedure time per lesion (95% CI), *s*	94.4 (87.1 to 101.7)	59.6 (54.0 to 65.2)	<0.001
Minor bleeding-related polypectomy, *n/N (% [95% CI])*			
Intraprocedural bleeding requiring endoscopic hemostasis	11/286 (3.8 [1.6 to 6.1])	23/325 (7.1 [4.3 to 9.9])	0.111
Hematochezia after polypectomy without hemostasis	7/83 (8.4 [2.5 to 14.4])	10/85 (11.9 [5.0 to 18.8])	0.61
Mean hospital stay (95% CI), *d*	5.1 (4.2 to 6.1)	2.9 (1.8 to 4.0)	0.003
Patients receiving warfarin	9.6 (8.1 to 11.1)	2.0 (1.6 to 2.3)	<0.001
Patients receiving DOACs	3.2 (2.5 to 3.9)	3.4 (1.7 to 5.1)	0.82
Adverse events, *n (%)**			
Abdominal pain	3 (3.6)	2 (2.4)	0.68
Bloating	4 (4.8)	2 (2.4)	0.44
Diarrhea	5 (6.0)	9 (10.7)	0.40
Any	9 (10.8)	11 (13.1)	0.81

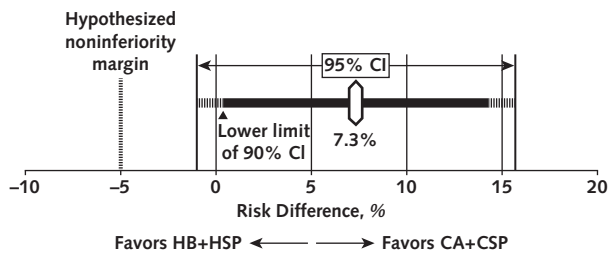
CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; DOACs = direct oral anticoagulants; HB = heparin bridging; HSP = hot snare polypectomy.
* Based on responses to patient survey. Data are missing for 1 patient.

polypectomy hemorrhage requiring endoscopic hemostasis. Even after protocol deviation cases were excluded (PPS analysis), the incidence of major bleeding was 12.7% (CI, 5.3% to 20.0%) in the HB+HSP group and 4.7% (CI, 0.2% to 9.2%) in the CA+CSP group. The intergroup difference was +8.0% (CI, −0.7% to 16.6%). Although 14 patients were excluded from the FAS analysis, 8 with ineligible lesions discovered after enrollment received treatment individually, none of whom had postpolypectomy bleeding. Outcomes for the other 6 patients are not available, because 2 declined to participate after enrollment and 4 did not have colonoscopy.

Although none of the patients in the CA+CSP group who were receiving warfarin had major bleeding, 4 patients in that group who were receiving DOACs did. Intraprocedural bleeding requiring endoscopic hemostasis immediately after polyp excision and postpolypectomy hematochezia without endoscopic hemostasis occurred more frequently in the CA+CSP than in the HB+HSP group, although these differences were not significant (Table 3). Characteristics of postpolypectomy bleeding cases are shown in Appendix Table 3 (available at Annals.org). Rivaroxaban use, more than 3 polyps removed, polyps larger than 6 mm, polyps in the right versus left colon, and protruded polyps were observed frequently in bleeding cases. In all 7 patients in the HB+HSP group who were receiving DOACs and had postpolypectomy bleeding, the bleeding occurred after HB was terminated.

Mean procedure time per lesion was significantly shorter in the CA+CSP than in the HB+HSP group. Because all polyps were not removed in 5 cases, the number of colonoscopies performed before all detected polyps were removed could not be assessed accurately. However, the mean hospitalization period was longer in the HB+HSP than in the CA+CSP group (Table 3).

Figure 2. Primary end point of the trial (difference in incidence of polypectomy-related major bleeding between groups).



CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; HB = heparin bridging; HSP = hot snare polypectomy.

Adverse Events

Localized peritonitis after polypectomy occurred in a patient in the HB+HSP group who had a 40-mm polyp and was excluded from the FAS. No thromboembolic events occurred. Other polypectomy-related adverse events obtained from patient survey forms were not significantly different between the 2 groups. All but 1 of the patient surveys (167 of 168) were completed, for a 99% response rate.

DISCUSSION

In this trial, we demonstrated the noninferiority of a new strategy for subcentimeter colorectal polyps (CA+CSP) com-

pared with a conventional approach (HB+HSP). Noninferiority also was shown in patients taking warfarin as well as those receiving DOACs. Because this study was a clinical trial, we aimed to reduce the risk for embolic events to the extent possible and believed that the risk for bleeding with HB should be compared with that of CA, although most of our patients had a low risk for atrial fibrillation and current guidelines do not recommend HB for such patients (10). Therefore, we used either HB or CA, rather than discontinuing anticoagulant therapy. Cold snare polypectomy with CA may become a standard approach for removing subcentimeter colorectal polyps in patients receiving anticoagulants, especially high-risk patients who cannot stop anticoagulant therapy, because HB+HSP requires a longer procedure time and hospital stay and carries the risk for loss of anticoagulation control during the transition from oral anticoagulants to heparin. Our results are consistent with current guidelines, which recommend CSP for subcentimeter polyps and do not recommend HB (10, 14, 15).

In theory, endoscopic procedures in patients receiving oral anticoagulants may be associated with hemorrhagic complications, but the incidence of severe bleeding in the CA+CSP group in our trial was 4.7%, which may be considered acceptable. Another RCT found a lower bleeding rate with CSP than with HSP in patients receiving warfarin (18). In contrast to our trial, in which patients received continuous DOAC therapy and underwent CSP, Radaelli and colleagues (25) reported a higher incidence of delayed major bleeding (14.3%) in patients who had high-risk endoscopic procedures and resumed DOAC therapy earlier than recommended by guidelines (10). Furthermore, we noted a higher number of total and right-sided polyps in the CA+CSP group, both of which may result in more frequent bleeding episodes, which suggests that CA+CSP may be a relatively safe approach. Therefore, we think that CSP may be the least risky polypectomy procedure. In addition, CA+CSP required a significantly shorter procedure time and hospital stay. Our results indicate not only the noninferiority but also the superiority of CA+CSP to HB+HSP.

In this trial, intraprocedural bleeding requiring endoscopic hemostasis was manageable in both groups. Because intraprocedural bleeding may depend on a patient's hemostatic ability, it may be associated with anticoagulant therapy before polypectomy (25). According to Western guidelines, anticoagulant therapy can be discontinued before an endoscopic procedure in patients at low risk for thrombosis (10, 13), and the absolute risk for an embolic event in patients whose anticoagulation is withdrawn for 4 to 7 days is reported to be approximately 1% (26, 27). However, embolic events may be severe once they occur. Therefore, the Japanese guidelines consider all patients receiving anticoagulants to be at high risk for thromboembolism associated with antithrombotic withdrawal (14). Our results suggest that discontinuing anticoagulant therapy before polypectomy for subcentimeter polyps may be unnecessary and support the Japanese guidelines, which recommend not withholding anticoagulants for procedures with low bleeding risk. On the contrary, because the anticoagulant effect of DOACs wanes within 12 to 24 hours after the last dose (28), delayed bleeding may be the result of reinitiating DOAC therapy too soon. Although current Western guidelines recommend DOAC cessation for several days after the procedure (10, 13), the risk for embolic events theoretically might be increased if DOACs are withheld for more than 48 hours (20, 29). An analysis of a nationwide database in Japan found a nonnegligible incidence of postendoscopy thromboembolism in patients receiving anticoagulants (30). In the current trial, most cases of postprocedural bleeding in the CA+CSP group occurred in patients receiving DOACs the day after polypectomy, suggesting that resuming DOAC therapy the next day was too soon. Therefore, a 1-day suspension of DOAC therapy after polypectomy, without prepolypectomy discontinuation, may be safer.

This trial had some limitations. First, clinicians and patients were not blinded to treatment allocation. However, blinding was not possible because clinicians had to actively monitor and assess patients for postprocedural complications, which may have been influenced by the anticoagulation approach and type of procedure. Second, we assessed 2 factors simultaneously, namely the management of anticoagulants and the polypectomy method used. Drawing a conclusion regarding which factor contributed to the results is difficult. Third, patients who were receiving DOACs before the study and were randomly assigned to HSP received HB during the trial to minimize their risk for an embolic event, although guidelines do not recommend this approach (6, 9). Fourth, we included patients with subcentimeter polyps only. Future research should investigate the appropriate management for patients with polyps 10 mm or larger. Finally, we could not assess differences in outcomes according to the kinds of DOACs used in this trial, because the number of patients using each DOAC type was too small.

In conclusion, CA+CSP for subcentimeter colorectal polyps in patients receiving anticoagulants did not increase the incidence of polypectomy-related major bleeding compared with HB+HSP and was associated with a shorter procedure time and hospital stay. Although CA+CSP is considered standard treatment for subcentimeter colorectal polyps in patients receiving anticoagulants, a larger trial is needed to identify a better management strategy for patients receiving DOACs.

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Data Sharing Statement: The following data will be made available with publication: complete deidentified patient data set (contact Yoji Takeuchi; e-mail, takeuti-yo@mc.pref.osaka.jp or yoji.endoscopy@oici.jp). The following supporting documents will be made available with publication: analytic/statistical code (contact Yoji Takeuchi; e-mail, takeuti-yo@mc.pref.osaka.jp or yoji.endoscopy@oici.jp). These data will be made available for any purpose to researchers whose proposed use of the data has been approved.

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Appendix 2: Exclusion Criteria

Patients with lesions 10 mm or larger, lesions suspected to be cancerous, pedunculated polyps, or depressed polyps were excluded from the study. Other exclusion criteria were previous enrollment in this trial, inflammatory bowel disease or familial polyposis, systemic administration of steroids or multiple-anticoagulant therapy, blood coagulation disorders, pregnancy or breastfeeding, psychiatric disease or symptoms that may have caused difficulty in participating in the trial, active bacterial or fungal infection, poorly controlled high blood pressure, respiratory disease requiring continuous oxygen therapy, dialysis, and a colonoscopist's judgment that the patient was not a candidate for enrollment.

Appendix 3: Anticoagulant Management

Perioperative anticoagulant management in this trial is detailed in the Appendix Figure.

Patients receiving warfarin in the HB+HSP group discontinued treatment 3 days before the scheduled day of polypectomy on an inpatient basis to start HB. Patients receiving DOACs in the HB+HSP group discontinued treatment 24 to 48 hours before the scheduled polypectomy; patients receiving twice-daily DOACs started HB 12 hours after cessation, and those with a once-daily regimen began HB 24 hours after cessation. The method for HB was as follows: Because low-molecular-weight heparin for subcutaneous injection was not officially approved in Japan for commercial use until recently, continuous intravenous infusion of unfractionated heparin, 10 000 to 20 000 U/d at 200 U/kg per day, was given, and the dosage was adjusted to achieve an activated partial thromboplastin time at least 1.5- to 2.0-fold greater than baseline. On the day of polypectomy, heparin was withdrawn 3 hours before the procedure and reinitiated 3 hours after completion. If no signs of bleeding were observed, warfarin or DOAC therapy resumed the next morning. The dosage for reinitiation was the same as before discontinuation. For patients receiving DOACs, HB was discontinued just after reinitiation of anticoagulant therapy. For those receiving warfarin, blood tests were performed at least once every second day to ensure that the PT-INR was in the therapeutic range before heparin was withdrawn.

In contrast, patients in the CA+CSP group, whether receiving warfarin or DOACs, continued their anticoagulant therapy before and after polypectomy as usual. Polypectomy for patients receiving DOACs in this group was scheduled after 3:00 p.m. to avoid peak DOAC levels 2 to 6 hours after oral administration. Because this trial's interventions were anticoagulant management during hospitalization and polypectomy, adherence to anticoagulant therapy was controlled by nurses at each hospital.

Appendix 4: Bowel Preparation, Prescribed Agents, Procedures Performed, Information Collected, Devices Used, and Management of Pathologic Assessment

Bowel preparation was performed according to each institution's protocol. Typically, patients were given a low-fiber diet and received preparative medication the day before colonoscopy: 160 mg of sennoside (Yodel-S [Fujimoto Pharmaceutical]) after every meal and 34 g of magnesium citrate (Magcorol P [Horii Pharmaceutical]) dissolved in 180 mL of water at night. The morning of colonoscopy, bowel cleansing was performed with 68 g of magnesium citrate dissolved in 1.8 L of water or 137.155 to 274.31 g of polyethylene glycol (Muben [Nihon Pharmaceutical] or Niflec or Moviprep [Eisai]) dissolved in 2 to 4 L of water (32, 33). Midazolam or diazepam with or without additional pethidine hydrochloride was used for sedation, according to patient preference. Scopolamine butylbromide or glucagon was administered as an antispasmodic agent. In each case, the investigation began after the

colonoscopist reached the cecum. In the event of incomplete colonoscopy, or in postcolectomy cases, any lesions detected in the limited area observed also were included.

For all detected lesions, location (right colon [cecum, ascending colon, and transverse colon], left colon [descending and sigmoid colon], or rectum), size (actual size and category [1 to 5 mm, 6 to 9 mm, or ≥10 mm]), and macroscopic type according to the Paris classification (34, 35) (polypoid [0-I] or nonpolypoid [0-II]) were documented. Polyp size was estimated visually by using the size of the snare as a reference. In general, all detected lesions were removed by the allocated method. In the HB+HSP group, submucosal injection before polypectomy was permitted. Electrocautery setting and type of snare were not standardized, and HSP was performed according to the clinical practice of each institution. For the CA+CSP group, the Exacto (US Endoscopy), Captivator II (Boston Scientific), or Profile (Boston Scientific) snare was recommended for polyp excision without electrocautery. Macroscopically identified residuals were excised by additional CSP, or by cold forceps polypectomy using standard or jumbo biopsy forceps. Polyps that could not be eradicated by conventional CSP were removed by piecemeal CSP. All removed polyps were retrieved, and the fixed specimens were subjected to histologic examination. The reference standard was histopathology with hematoxylin and eosin staining. Histopathologists at each institution diagnosed all specimens according to the Japanese classification for colorectal carcinoma (36). Colonoscopists adhered to cancer screening guidelines for polypectomy.

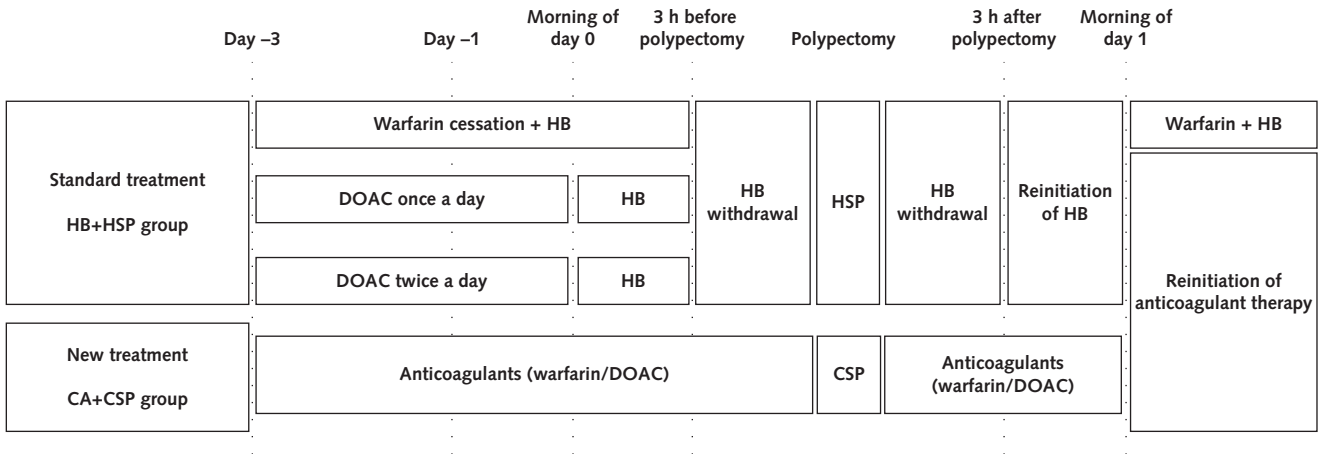
Appendix 5: Details Regarding Data Collection

The case report form (CRF) consisted of 7 pages: a patient eligibility checklist, including the confirmation date for eligibility; patient background information; procedural outcomes from hospitalization until completion of polypectomy; procedural outcomes after polypectomy until discharge; follow-up data reporting all events from polypectomy to 28 days or more after the procedure, including the patient survey form, which was returned 28 days after polypectomy or later; adverse events; and a discontinuation reporting form. Nonblinded investigators were encouraged to send these data as soon as possible to an independent data center (Medical Research Support, Kyoto, Japan) when each page of the CRF was completed. Because the follow-up data included the patient survey form, both the follow-up data sheet and survey form were returned 28 days after polypectomy, and information about all events during the 28 days after polypectomy was collected. Finally, the data center reminded each institution to send all CRFs by April 2018.

Appendix 6: Details Regarding Statistical Analysis

The independent data center, Medical Research Support, managed the study and was responsible for study coordination, randomization, and maintenance of the study database and data collection. The Center for Translational Research at the Institute of Medical Science Hospital of the University of Tokyo was responsible for data analysis.

Appendix Figure. Schedules of periprocedural management of anticoagulant therapy in both groups.



CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; DOAC = direct oral anticoagulant; HB = heparin bridging; HSP = hot snare polypectomy.

Appendix Table 1. Perioperative Anticoagulant Management

Measure	Study Group		*P* Value
	HB+HSP	CA+CSP	
Median time off of anticoagulant therapy (IQR), *d*			
Patients receiving warfarin	4 (4–4)	–	
Patients receiving DOACs	2 (1–2)	–	
Mean laboratory values the morning of polypectomy (SDs)			
PT-INR ratio			
Patients receiving warfarin	1.25 (0.17)	2.01 (0.42)	<0.001
Patients receiving DOACs	1.06 (0.08)	1.17 (0.15)	<0.001
aPTT, *s*			
Patients receiving warfarin	46.6 (15.2)	40.9 (8.1)	0.078
Patients receiving DOACs	38.5 (11.6)	37.4 (7.5)	0.57
Median time before restarting HB (IQR), *h*	3 (3–3)	–	
Median time to postprocedure anticoagulant therapy (IQR), *d*	1 (1–1)	–	
Mean laboratory values the morning after polypectomy (SDs)			
Hemoglobin level, *g/L*	135 (16)	139 (17)*	0.170
Platelet count, × 10^9 *cells/L*	190 (56)	191 (53)*	0.87
PT-INR ratio			
Patients receiving warfarin	1.17 (0.14)	2.04 (0.45)	<0.001
Patients receiving DOACs	1.10 (0.15)	1.15 (0.13)*	0.080
aPTT, *s*			
Patients receiving warfarin	47.4 (15.4)	42.2 (8.4)	0.144
Patients receiving DOACs	40.2 (13.9)	36.3 (6.7)*	0.054
Median time for HB after polypectomy (IQR), *d*			
Patients receiving warfarin	4 (2.5–7)	–	
Patients receiving DOACs	1 (1–1)	–	

aPTT = activated partial thromboplastin time; CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; DOACs = direct oral anticoagulants; HB = heparin bridging; HSP = hot snare polypectomy; INR = international normalized ratio; IQR = interquartile range; PT = prothrombin time.
* Data are missing for 2 patients.

Appendix Table 2. Additional Information on Baseline Characteristics of the Full Analysis Set

Characteristics	Study Group	
	HB+HSP (*n* = 83)	CA+CSP (*n* = 85)
Participants enrolled at each institution, *n*		
Osaka International Cancer Institute	14	14
Kurashiki Central Hospital	9	9
Suita Municipal Hospital	7	7
Ishikawa Prefectural Central Hospital	7	6
Akashi Medical Center	7	6
Osaka City General Hospital	7	3
Sapporo Medical Center NTT EC	4	3
National Hospital Organization Tokyo Medical Center	3	3
Sano Hospital	3	3
Kindai University Faculty of Medicine	3	3
Japanese Red Cross Society Wakayama Medical Center	3	3
National Hospital Organization Osaka National Hospital	4	2
Nihon University School of Medicine	3	3
Tane General Hospital	1	4
Kyoto Second Red Cross Hospital	1	3
Shizuoka Cancer Center	1	3
Utsunomiya Memorial Hospital	3	1
Kansai Rosai Hospital	1	2
Naha City Hospital	1	2
Nara City Hospital	0	2
Kumamoto University	0	2
Osaka General Medical Center	1	0
Hyogo College of Medicine	0	0
Tochigi Cancer Center	0	1
Teine Keijinkai Hospital	0	0
Sapporo Higashi Tokushukai Hospital	0	0
National Cancer Center Hospital	0	0
National Hospital Organization Kyushu Medical Center	0	0
Cancer Institute Hospital	0	0
Reason for anticoagulant therapy, *n (%)**		
Atrial fibrillation	66 (80)	68 (80)
Deep venous thrombosis	8 (10)	7 (8)
Valve replacement	5 (6)	4 (5)
Cerebral infarction	5 (6)	9 (10)
Peripheral vein diseases	2 (2)	2 (2)
Pacemaker replacement	1 (1)	1 (1)

CA = continuous administration of oral anticoagulants; CSP = cold snare polypectomy; HB = heparin bridging; HSP = hot snare polypectomy; NTT EC = Nippon Telegraph and Telephone East Corporation.
* More than 1 reason may have been given.

Appendix Table 3. Characteristics of Patients With Postpolypectomy Bleeding

Case	Age, *y*	Sex	Anticoagulant	Antiplatelet	CCI Score	Treatment Group	PT-INR Ratio*	aPTT, *s**	Polyps, *n*	Maximum Polyp Size, *mm*	Polyp Location, *n*	Paris Classification of Polyps, *n*	Days of Bleeding, *n*
1	70	Male	Warfarin	–	0	HB+HSP	1.16	49.8	13	9	Right colon: 7 Left colon: 6	0-I: 7 0-IIa: 6	6 (during HB)
2	79	Male	Rivaroxaban	–	2	HB+HSP	1.15	44.7	13	9	Right colon: 7 Left colon: 6	0-I: 9 0-IIa: 4	4 (after HB)
3	73	Male	Dabigatran	–	1	HB+HSP	1.12	36	3	5	Right colon: 2 Left colon: 1	0-I: 3 0-IIa: 0	3 (after HB)
4	73	Male	Warfarin	Sarpogrelate	0	HB+HSP	1.08	42.6	4	8	Right colon: 4 Left colon: 0	0-I: 3 0-IIa: 1	1 (during HB)
5	68	Female	Warfarin	–	0	HB+HSP	1.06	45.4	3	8	Right colon: 2 Left colon: 1	0-I: 3 0-IIa: 0	1 (during HB)
6	61	Male	Rivaroxaban	–	0	HB+HSP	1.08	36.4	1	7	Right colon: 0 Left colon: 1	0-I: 1 0-IIa: 0	2 (after HB)
7	75	Male	Rivaroxaban	–	0	HB+HSP	1.06	40.1	1	6	Right colon: 1 Left colon: 0	0-I: 1 0-IIa: 0	2 (after HB)
8	72	Male	Edoxaban	–	0	CA+CSP	1.11	33.6	1	8	Right colon: 1 Left colon: 0	0-I: 1 0-IIa: 0	4
9	68	Male	Rivaroxaban	–	0	CA+CSP	1.03	37.9	4	7	Right colon: 4 Left colon: 0	0-I: 4 0-IIa: 0	1
10	56	Male	Rivaroxaban	–	0	HB+HSP	0.98	27.9	3	3	Right colon: 3 Left colon: 0	0-I: 3 0-IIa: 0	1 (after HB)
11	49	Male	Rivaroxaban	–	0	HB+HSP	1.01	31.9	4	7	Right colon: 3 Left colon: 1	0-I: 2 0-IIa: 2	4 (after HB)
12	64	Male	Apixaban	–	0	CA+CSP	1.00	27	3	5	Right colon: 0 Left colon: 3	0-I: 0 0-IIa: 3	1
13	65	Male	Rivaroxaban	–	0	CA+CSP	1.01	38.7	4	6	Right colon: 3 Left colon: 1	0-I: 0 0-IIa: 4	1
14	74	Female	Rivaroxaban	–	1	HB+HSP	1.09	37.2	6	8	Right colon: 2 Left colon: 4	0-I: 6 0-IIa: 0	4 (after HB)

aPTT = activated partial thromboplastin time; CA = continuous administration of oral anticoagulants; CCI = Charlson Comorbidity Index; CSP = cold snare polypectomy; HB = heparin bridging; HSP = hot snare polypectomy; INR = international normalized ratio; PT = prothrombin time.
* Next morning.

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