Original Article

Impact of clinical characteristics of colonic diverticular bleeding in extremely elderly patients treated with direct oral anti-coagulant drugs: a retrospective multi-center study

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(Received 24 August, 2020; Accepted 25 October, 2020; Published online 3 April, 2021)

Since there were no available data about colonic diverticular bleeding in extremely elderly patients (>80 years old) treated with direct oral anticoagulants (DOACs), we tried to determine clinical characteristics in those with colonic diverticular bleeding taking DOACs and to compare clinical outcomes of those in DOAC-treated to those in warfarin-treated . We enrolled DOAC-treated (*n* = 20) and warfarin-treated (*n* = 23) extremely elderly patients with diverticular bleeding diagnosed by colonoscopy. We performed a retrospective review of patients' medical charts and endoscopic findings. We classified colonic diverticular bleeding based on endoscopic features due to modified previous study following three groups, type A (active bleeding), type B (non-active bleeding) and type C (bleeding suspected). Clinical outcomes such as number of recurrent bleeding, thrombotic events and mortality were estimated. There were no differences in endoscopical features and clinical characteristics between patients treated with DOAC and warfarin therapy. However, the number of recurrent bleeding, frequency of required blood transfusions and units of blood transfusion in warfarin-treated patients were significantly higher ($p<0.05$) compared to those in DOAC-treated groups. In addition, mortality and thrombotic events did not differ between DOAC- and warfarin-treated patients. Clinical outcomes suggest that DOACs can be recommended for extremely elderly patients with colonic diverticular disease.

***Key Words*:** **colonic diverticular bleeding, direct oral anti-coagulant drugs, extremely elderly patients**

In recent years, a new type of oral anticoagulants, direct oral anticoagulants (DOACs) with direct inhibition of factor IIa (dabigatran) or Xa (rivaroxaban, apixaban, edoxaban) have shown superiority or noninferiority to warfarin for the treatment and prevention of stroke in atrial fibrillation (AF) and show a more promising safety profile with respect to the important outcome of bleeding.[1–3] DOACs seem to offer several advantages over warfarin, including rapid onset of action, few drugs and food interactions, and predictable pharmacokinetics, apparently eliminating the requirement for regular coagulation monitoring.[4] Thus, DOACs are prescribed at a fixed dose without the need of monitoring or dose adjustment because of their rapid effect as anticoagulants and their short half-life. However, a number of studies investigating bleeding risk through the use of DOACs vs other anticoagulants such as the EINSTEIN-DVT and EINSTEIN-PE studies as well as the ROCKET-AF trial, have shown a statistically significant increase in GI bleeding in patients treated with DOACs.[3,5,6] In addition, several studies have reported risk factors for GI bleeding after therapeutic gastrointestinal endoscopy in patients receiving DOACs and warfarin.[7–10] Kubo *et al.*[7] have reported that delayed bleeding rates after endoscopic submucosal dissection (ESD) procedures were not significantly different between patients receiving DOACs and warfarin.

Although colonic diverticular bleeding ceases spontaneously in 70% to 90% of cases, approximately 4% of patients with colonic diverticulosis suffer from severe diverticular bleeding.[11] Therefore, understanding the risk factors for diverticular bleeding is critical for guiding the clinical management and important for elderly patients. The prevalence of colonic diverticular bleeding is increasing due to the rising incidence of colonic diverticulosis and antithrombotic drug usage.[12] However, there are currently no available data on colonic diverticular bleeding in extremely elderly patients treated with DOACs. Since elderly and extremely elderly patients are at higher risk of various complications such as cardiovascular disease and cerebral infarction, DOAC-induced gastrointestinal bleedings were seemed to be critical for elderly patients and extremely elderly patients. There were no available data about the precise mechanisms of mucosal injuries and pharmacokinetics in the patients treated with DOAC, especially in the extremely elderly patients. In this multi-center study, we evaluated clinical characteristic and risk factors of the extremely elderly patients (more than 80 years old) with colonic diverticular bleeding taking DOAC and compared clinical outcomes such as recurrent bleeding and sum of blood transfusion in these patients against patients on warfarin therapy.

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doi: 10.3164/jcbn.20-140

Materials and Methods

Statement of Ethics. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Review Committee of Nippon Medical School Hospital (511-3-27), University of Tokyo (2018007), Juntendo University School of Medicine (2018078), Teikyo University School of Medicine (351-27), Nippon Medical School Musashikosugi Hospital (455-30-26), and Tama-Hokubu Medical Center (34-21). Written informed consent was obtained from subjects prior to the enrollment of this study.

Patients. Participants in our multi-center retrospective study comprised forty-three consecutive patients undergoing colonoscopy who were on anticoagulant therapies, including warfarin and DOACs, at the following seven participating institutions from April 2015 to October 2019; Nippon Medical School Musashi Kosugi Hospital (Division of Gastroenterology, Division of Surgery), Nippon Medical School Hospital, Tokyo University Hospital, Teikyo University Hospital, Juntendo Medical School Hospital, and Tama-Hokubu Medical Center. We enrolled DOAC-treated [ivaroxaban (n = 8), apixaban (n = 6), edoxaban (n = 4), dabigatran (n = 2), n = 20] and warfarin-treated (n = 23) extremely elderly patients (>80 years old) with diverticular bleeding diagnosed by colonoscopy (Fig. 1). Exclusion criteria included severe systemic illness such as chronic hemodialysis, peritoneal dialysis, pulmonary failure, and malignant diseases. All patients gave informed written consent prior to enrollment.

Data sources and measurements. Patient information was obtained from patient electronic medical records, and included age, sex, body mass index (BMI), comorbidities at admission, and drugs used. We determined the presence or absence of five comorbidities at admission, congestive heart failure, myocardial infarction, cerebrovascular disease, hypertension, and diabetes mellitus. We also assessed the use of low-dose aspirin, thienopyridines, other antiplatelet drugs, and non-steroidal anti-inflammatory drugs. Anticoagulants included warfarin and DOACs (rivaroxaban, apixaban, dabigatran, and edoxaban).

Assessment of colonic diverticular bleeding. Detection of active bleeding was determined by colonoscopy after bleeding episode was occurred. We classified colonic diverticular bleeding into three groups based on the visibility of the source of bleeding according to a modified previous study;[13] type A, active bleeding as manifested by spurting bleeding from a diverticulum or a massive hematin attached to the base of a diverticulum; type B, non-active bleeding as determined by identification of the potential bleeding source such as visible blood vessels or a black spot without active bleeding at the base of the diverticulum; and type C, dynamic CT were performed prior to colonscopy and bleeding point in the colon will be presumptive. Although presumptive diverticular bleeding with the presence of a blood clot in the colon were suspected, no bleeding diverticulum isolated. We excluded lower intestinal bleeding without diverticular bleeding.

Assessment of clinical outcome. Clinical outcomes such as the rebleeding events (rebleeding, number of recurrent bleeding, required blood transfusion, units of blood transfusion, and period of hospitalization), thromboid events, the ratio of withdrawal of anticoagulant drugs, and mortality were estimated. The number of recurrent bleeding episodes was defined as the frequency of performing colonoscopy examinations needed to detect the origin of rebleeding in the same hospitalization. The ratio of rebleeding was determined by the occurrence of rebleeding within 30 days after admission.

Statistical analysis. For statistical evaluation of group data, Students' t test for paired data and analysis of variance (ANOVA) for multiple comparisons were followed by Scheffe's F test. The Mann-Whitney U test and χ^2 test was used for analysis of categorical data. Data analyses were performed with EZR,[14] which is for R. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. A p value of less than 0.05 was statistically significant.

Results

Comparison of endoscopic findings between DOAC-treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients with it. Endoscopic findings for colonic diverticular bleeding were divided into three group subtypes according to extent of bleeding based on a modified previous study; type A, active bleeding; type B, non-active bleeding; and type C, presumptive bleeding (Fig. 2A–C). There was no significant difference in the endoscopical appearance of active bleeding between DOAC-

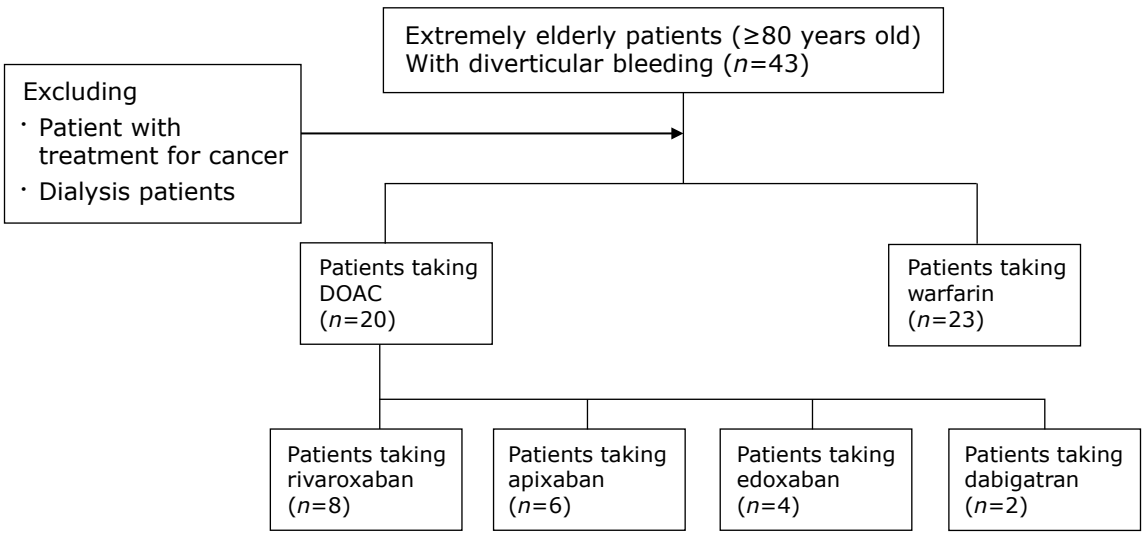

Fig. 1. Protocohol of the study.

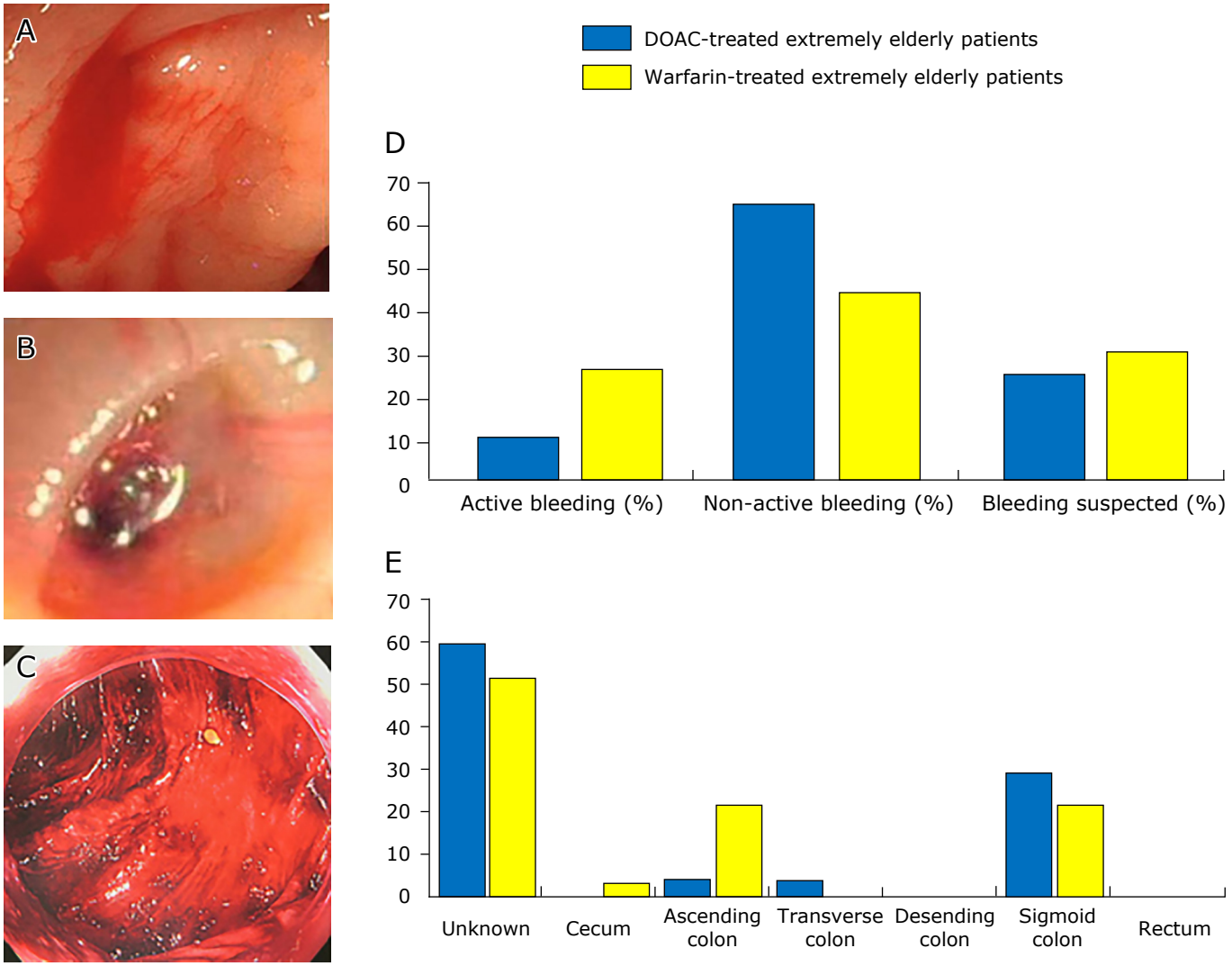

Fig. 2. Comparison of endoscopical appearance and localization of bleeding point between DOAC-treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients with it. (A) Endoscopical appearances for colonic diverticular bleeding were determined as active bleeding. (B) Endoscopical appearances for colonic diverticular bleeding were determined as non-active bleeding. (C) Endoscopical appearances for colonic diverticular bleeding were determined as bleeding suspected. (D) There was no significant difference in the endoscopical appearance of active bleeding between DOAC-treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients with it. (E) There were no significant differences in the location of bleeding points such as sigmoid colon, descending colon, transverse colon, ascending colon between two groups. See color figure in the on-line version.

treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients with it (Fig. 2D). Then, there were also no significant differences in the precise location of bleeding diverticula in the colon, including the sigmoid colon, descending colon, transverse colon, ascending colon between the two groups (Fig. 2E).

Comparison of clinical characteristics of DOAC-treated extremely elderly patients with colonic diverticular bleeding with warfarin-treated extremely elderly patients with it. There were no significant differences in age, sex and BMI between DOAC-treated extremely elderly patients and warfarin-treated extremely elderly patients (Table 1). There were also no significant differences in comorbidities such as CHF, OMI, CVA, HT, and DM between DOAC-treated extremely elderly patients and warfarin-treated extremely elderly patients (Table 1). In addition, there were no significant differences in the proportion of patients taking NSAIDs or low dose aspirin between DOAC-treated extremely elderly patients and warfarin-treated extremely elderly patients (Table 1).

Comparison of clinical data in patients with DOAC-treated extremely elderly patients with warfarin-treated extremely elderly patients. Creatinine and eGFR (1.49 ± 0.75, 37.3 ± 11.7) in warfarin-treated extremely elderly patients were significantly ($p<0.05$) aggravated compared to those (1.06 ± 0.36, 52.7 ± 23.1) in DOAC-treated extremely elderly patients (Table 2). In addition, coagulation factors such as prothrombin time (PT) and PT-international normalized ratio (INR) (39.9 ± 20.5, 2.23 ± 0.98) were significantly ($p<0.05$) aggravated in warfarin-treated extremely elderly patients compared to those (61.9 ± 17.8, 1.44 ± 0.34) in DOAC-treated extremely elderly patients (Table 2). There was no a significant difference in the ratio of detection of extravasation using enhanced CT scan between DOAC-treated extremely elderly patients and warfarin-treated extremely elderly patients (Table 2).

doi: 10.3164/jcbn.20-140

Table 1. Comparison of clinical characetristics of DOAC-treated extremely elderly patients with colonic diverticular bleeding with warfarin-treated extremely elderly patients with it

		DOAC-treated extremely elderly patients (n = 20)	Warfarin-treated extremely elderly patients (n = 23)	p value
Age, median (range)		85 (80–93)	86 (80–98)	0.62
Sex (male/female) (n)		16/4	15/8	0.99
ASA-PS (%)		I:II:III:IV:V:VI = 5:50:45:0:0:0	I:II:III:IV:V:VI = 4:65:31:0:0:0	0.60
BMI		22.0 ± 3.84	22.6 ± 3.61	0.65
Smoking (%)		4 (20%)	6 (26%)	1.00
Alcohol (%)		2 (10%)	9 (39%)	0.06
Comorbidity	CHF n (%)	13 (65%)	13 (57%)	0.80
	OMI n (%)	5 (25%)	9 (39%)	0.51
	CVA n (%)	5 (25%)	3 (13%)	0.54
	HT n (%)	17(85%)	16 (70%)	0.41
	DM n (%)	6 (3%)	5 (22%)	0.79
The ratio of taking NSAIDs		1 (5%)	5 (22%)	0.26
The ratio of taking LDA		4 (20%)	9 (39%)	0.30

DOAC, direct oral anti-coagulant drug; LDA, low dose aspirin.

Table 2. Comparison of clinical data in patients with DOAC-treated extremely elderly patients with warfarin-treated extremely elderly patients

	DOAC-treated extremely elderly patients (n = 20)	Warfarin-treated extremely elderly patients (n = 23)	p value
WBC ($\times 10^3/\mu l$)	5.33 ± 1.51	7.45 ± 2.03	<0.05
Hb (g/dl)	9.51 ± 2.17	9.30 ± 2.85	0.78
Plt ($\times 10^4/\mu l$)	21.0 ± 6.26	20.7 ± 7.6	0.80
BUN (mg/dl)	25.5 ± 9.88	33.0 ± 16.2	0.08
Cr (mg/dl)	1.06 ± 0.36	1.49 ± 0.75	<0.05
eGFR (ml/min/1.73 m^2)	52.7 ± 23.1	37.3 ± 11.7	<0.05
CRP (mg/dl)	1.86 ± 5.24	0.94 ± 1.99	0.45
Alb (g/dl)	3.46 ± 0.42	3.17 ± 0.50	0.06
PT (%)	61.9 ± 17.8	39.9 ± 20.5	<0.05
PT-INR	1.44 ± 0.34	2.23 ± 0.98	<0.05
APTT (s)	37.0 ± 4.40	35.0 ± 5.55	0.27
D-dimer (μg/ml)	3.08 ± 5.17	1.84 ± 2.36	0.54
Extravasation, n (%)	1 (5%)	5 (22%)	0.19

DOAC, direct oral anti-coagulant drug.

Comparison of frequency of recurrent bleeding and the ratio of blood transfusion between DOAC-treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients. The number of recurrent bleeding (1.10 ± 0.45) in DOAC-treated extremely elderly patients was significantly (p<0.05) lower compared to that (2.78 ± 2.49) in warfarin-treated extremely elderly patients (Table 3). In contrast, the ratio of rebleeding as the occurrence of rebleeding within 30 days after admission in DOAC-treated extremely elderly patients was zero percentage and that in warfarin-treated extremely elderly patients was also low level (8.7%) (Table 3). In addition, the ratio of required blood transfusion (60%) and required units of blood transfusion (4.17 ± 5.29) in warfarin-treated extremely elderly patients were significantly higher compared to those (25%, 1.30 ± 2.70) in DOAC-treated extremely elderly patients (Table 3). There were no significant differences in the ratio of withdrawal of distinct drugs between DOAC- and warfarin-treated extremely elderly patients (Table 3). Although the ratios of withdrawal were high (95% and 74%, respectively) in both DOAC-treated and warfarin-treated extremely elderly patients, mortality and thrombotic events in both groups were zero percent. Interestingly, there was no statistically significant differences in mortality rate between DOAC-treated extremely elderly patients with colonic diverticular bleeding and warfarin-treated extremely elderly patients with it. Endoscopical clipping were performed in 7 DOAC-treated extremely elderly patients and 9 warfarin-treated extremely elderly patients for endoscopical haemostasis (Table 3). In addition, one patients treated with endoscopical clipping was operated and interventional radiology were not undertaken for haemostasis in enrolled patients.

Table 3. Comparison of hemostasis and clinical outcomes between DOAC-treated extremely elderly patients and warfarin-treated extremely elderly patients

	DOAC-treated extremely elderly patients (n = 20)	Warfarin-treated extremely elderly patients (n = 23)	p value
Hemostasis, n (%)	7 (35%)	9 (39%)	1.00
Clipping, n (%)	7 (35%)	9 (39%)	1.00
Interventional radiology, n (%)	0 (0%)	0 (0%)	1.00
Operation, n (%)	0 (0%)	1 (4%)	1.00
Clinical Outcomes			
Rebleeding, n (%)	0 (0%)	2 (8.7%)	0.49
Number of recurrent bleeding, mean ± SD	1.10 ± 0.45	2.78 ± 2.49	<0.05
Required blood transfusion, n (%)	5 (25%)	14 (60%)	<0.05
Units of blood transfusion, mean ± SD	1.30 ± 2.70	4.17 ± 5.29	<0.05
Period of hospitalization, mean ± SD	17.9 ± 19.8	13.9 ± 10.1	0.40
Mortality, n (%)	0 (0%)	0 (0%)	1.00
Heparin bridging, n (%)	1 (5%)	4 (17.4%)	0.35
Thromboid events, n (%)	0 (0%)	0 (0%)	1.00
Withdrawal of drugs, n (%)	19 (95%)	17 (74%)	0.10
Period of withdrawal (days)	6.28 ± 6.70	4.55 ± 4.38	0.35
Retake, n (%)	16 (75%)	14 (61%)	0.20

DOAC, direct oral anti-coagulant drug.

Discussion

The major findings of this study are 1) we were first to report clinical characteristics of DOAC-treated extremely elderly patients with colonic diverticular bleeding and there were no significant differences in clinical characteristics between DOAC-treated and warfarin-treated extremely elderly patients, 2) the number of recurrent bleeding, ratio of required blood transfusions and required units of blood transfusion in warfarin-treated extremely elderly patients were significantly higher (p<0.05) compared to those in DOAC-treated extremely elderly patients, 3) there were no statistically significant differences in mortality and thrombotic events between DOAC-treated and warfarin-treated extremely elderly patients with colonic diverticular bleeding.

Colonic diverticular bleeding is the most common in acute lower gastrointestinal bleeding and is increasing in Japan.[15–19] Sengupta *et al.*[20] have reported that the proportion of DOAC-treated lower GI bleeding (42.6%, mostly of diverticular origin) was higher compared to that in the upper GI tract (26.9%). Previous studies have reported low rates of colonic diverticular bleeding among patients taking DOAC. However, few studies have reported the precise association between DOAC usage and risk of diverticular hemorrhage. Vajravelu *et al.*[21] have also reported that odds ratio of diverticular and warfarin-treated hemorrhage in DOAC-treated patients was 1.4 (237/14,925) and that the odds ratio of diverticular bleeding was dependent on age. In addition, the incidence rate of diverticular bleeding in elderly patients aged >80 years was significantly higher compared to that in 50–59 years patients.[21] Considering of previous study, it is critical issue to investigate DOAC-induced extremely elderly patients with diverticular bleeding. In this current multi-center study, we are first to report diverticular bleeding in extremely elderly patients treated with DOACs. Although Abraham *et al.*[22] have reported that GI bleeding in patients on DOAC therapy increased among patients >75 years old, our study demonstrates no statistically significant differences in clinical characteristics and bleeding rates between extremely elderly patients treated with DOAC and non-extremely elderly patients with it (data not shown). Sengupta *et al.*[20] have reported that age as well as thienopyridine use, prior history of gastrointestinal bleeding and resumption of a DOAC within 30 days were all associated with an increased rate of recurrent gastrointestinal bleeding. In our study, the proportion of active bleeding determined by colonoscopy in DOAC-treated extremely elderly patients was 10%. Although there existed a risk in performing the procedure in patients of advanced age, the use of colonoscopy to identify the precise bleeding points in patients with diverticular hemorrhages was critical in the management of diverticular bleeding in these elderly patients. In particular, considering that bleeding in the sigmoid colon of DOAC-treated extremely elderly patients was 75%, performance of sigmoidoscopy was vital in this cohort of patients. Since there is evidence suggesting that patients on DOAC therapy have an increased risk of non-procedure-related GI bleeding compared with patients receiving warfarin,[23,24] it is important to examine the colon to detect any bleeding points in extremely elderly patients being treated with DOACs.

Yokoyama *et al.*[25] have reported that in younger populations, the incidence of gastrointestinal hemorrhage was significantly higher in patients on warfarin therapy than patients on DOACs. Nagata *et al.*[26] have also reported that the risk of post-endoscopic procedure was higher in warfarin than DOAC users. In our study, we are first to compare clinical characteristics of extremely elderly patients treated with DOAC with a cohort of patients on warfarin therapy. In our data, there were no significant differences in sex and BMI between DOAC-treated and warfarin-treated extremely elderly patients with colonic diverticular bleeding. The frequency of recurrent bleeding, required blood transfusion and units of blood transfusion were significantly higher in the warfarin-treated extremely elderly patients than those in DOAC-treated extremely elderly patients. Since there were no differences in withdrawal of drugs between DOAC-treated and warfarin-treated cohort of patients described in Table 3, administration of warfarin in extremely elderly patients with worsened clinical conditions such as renal failure may be attributed to the higher frequency of recurrent bleeding and required blood transfusion units in

doi: 10.3164/jcbn.20-140

this cohort of patients. In addition, although one DOAC-treated and four warfarin-treated patients were started heparin bridging therapy after the cessation of DOAC or warfarin, only one patient with heparin bridging therapy after the cessation of warfarin had rebleeding within 30 days after admission. Further studies will be needed to clarify whether the cessation of DOAC or bridging anticoagulation in the patients with colonic diverticulum affected clinical outcomes including rebleeding as well as other anti-thrombotic drugs.[27,28] Park *et al.*[29] have also reported that DOAC-treated Asians with atrial fibrillation were associated with lower risks of recurrent stroke and GI bleeding compared to warfarin-treated Asians. Although Amin *et al.*[30] have also reported that apixaban had a lower risk of GI bleeding compared to warfarin, they have also reported that rivaroxaban had a higher risk of GI bleeding compared to that seen in warfarin. Considering of our results, treatment with DOAC was recommended for extremely elderly patients with colonic diverticular. Further studies are needed to compare clinical outcomes of GI-bleeding in warfarin-treated extremely elderly patients with those receiving respective DOACs including apixaban, rivaroxaban, edoxaban and dabigatran.

Moreover, our study found no statistically significant difference in the period of hospitalization between DOAC-treated and warfarin-treated extremely elderly patients. In contrast, Ng *et al.*[31] have reported the hospitalization rate was significantly higher in the warfarin-treated group compared to the DOAC-treated group. In addition, in our data there was not significant differences in mortality between DOAC-treated and warfarin-treated extremely elderly patients in spite of high ratios of discontinuation of oral anticoagulant therapy in both groups. Deutsch *et al.*[32] have reported mortality rate at the day 30 was relatively high (11.8%) in elderly patients treated with DOACs. They have reported that half of the cause of mortality was GI bleeding.[32] In contrast, Brodie *et al.*[33] have also reported that no death occurred at day 30 in an American retrospective cohort. We have first to report clinical outcomes including mortality and required units of blood transfusions in DOAC-treated or warfarin-treated extremely elderly patients with diverticular bleeding. Although the frequency of recurrent bleeding and required blood transfusion in the warfarin-treated extremely elderly patients were significantly higher compared to those in DOAC-treated extremely elderly patients, mortality rates in both groups were same. Although Brodie *et al.*[33] have reported that hemoglobin levels in warfarin-treated patients were significantly lower compared to those in DOAC-treated patients, there were not significant differences in hemoglobin levels between warfarin-treated and DOAC-treated extremely elderly patients in our study.

There were some limitations about this study. First, in this study, bleeding rates for patients taking DOAC or warfarin in extremely elderly patients with colonic diverticular bleeding were not estimated based on the consideration for total number of patients taking DOAC or warfarin. Secondly, the possibility that DOAC can be prescribed to selected patients without renal dysfunction may contribute to clinical outcomes including the reduction of mortality, the number of recurrent bleeding, the frequency of required blood transfusion.

Taken together, considering of clinical outcome such as mortality and number of recurrent bleeding and none of thrombotic events, DOAC usage for extremely elderly patients with colonic diverticulum will be recommended.

Author Contributions

KK: data collection, and writing the manuscript; YK, NU, SA, HY, YS, RN, NY, KI, MH, KM, TY, MW, MK, and KI: data collection, KG: revision of the manuscript, SF: data collection, direction of experiment, and writing the manuscript.

Acknowledgments

We thank Mrs. Habiro for editing the manuscript. The Ministry of Education, Culture, and Science and the Ministry of Health, Japan (16K09294) funded this study.

Conflicts of Interest

No potential conflicts of interest were disclosed.

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doi: 10.3164/jcbn.20-140