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Satisfactory Outcome with Low Activated Clotting Time (<150 Seconds) in Extracorporeal Membrane Oxygenation

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Abstract

Backgrounds: Optimal anticoagulation is critical for successful extracorporeal membrane oxygenation (ECMO). Activated Clotting Time (ACT) is a widely used laboratory parameter to monitor anticoagulation. The therapeutic range of ACT is 180 s-220 s. We investigated the effect of a lower target ACT (<150 sec) during ECMO on safety and outcomes and compared it with those of a conventional target ACT (180 s-200 s).

Study Design and Methods: In this retrospective study, we reviewed 72 patients treated with ECMO from March 2017 to October 2019. We included 43 patients after applying the exclusion criteria and divided them into the low ACT group (<150 s, n=14, 32.6%) and conventional ACT group (≥ 150 s, n=29, 67.4%).

Results: There was no difference in the successful weaning from ECMO support (50% *vs.* 62.1%, p=0.452) and discharge (50% *vs.* 41.4%, p=0.594) rates between the groups. A patient in the conventional ACT group had intracranial hemorrhage. There was no thromboembolic complication, except in one patient where an intra-circuit thrombus was observed.

Conclusion: A lower target ACT level did not increase the thromboembolic risk during ECMO management. Thus, clinicians may consider lower ACT management in patients at a high risk of hemorrhagic complications. Further randomized controlled are warranted to validate these results.

Keywords: Extracorporeal circulation; Extracorporeal cardiopulmonary resuscitation; Activated clotting time; Complication; Survival to discharge

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Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a supportive treatment that is increasingly being used for patients with critical respiratory and circulatory failure [1]. However, high mortality and morbidity rates are noted among patients receiving ECMO support, partly due to the complications associated ECMO itself. Adverse outcomes, like bleeding and thromboembolism, are inevitable due to the nature of the ECMO circuit components. Continuous anticoagulation is crucial during ECMO, and a fine balance must be maintained between these two potential risks.

Unfractionated Heparin (UFH) remains the mainstay for continuous anticoagulation therapy. The Activated Clotting Time (ACT) and activated Partial Thromboplastin Time (aPTT) are most commonly used to monitor heparin activity. Although therapeutic anticoagulation during ECMO is defined by an ACT of 180 s-220 s, [2] there is no consensus presently regarding the ACT value and the guidelines vary across different centers [3]. In case of active bleeding and thrombocytopenia, the heparin dose can be modified, and this leads to favorable outcomes [4-9]. In this study, we investigated the effect of a lower ACT target (<150 s) during ECMO management on safety and outcomes and compared the effects of this lower ACT with those of a conventional target ACT (180 s-200 s) during ECMO.

Material and Methods

After institutional review board approval (2020AS0038), the data were retrospectively collected from the electronic medical records. Patients aged >18 years who received Veno-Venous (VV) or Veno-Arterial (VA) ECMO support from March 2017 to October 2019 were initially included. From a total of 72 patients, 29 patients were excluded for the following reasons: cardiopulmonary bypass weaning failure in the operating room leading to postoperative ECMO support (n=10), ECMO support duration <24 h (n=7), and non-availability of ACT data (only aPTT was monitored;

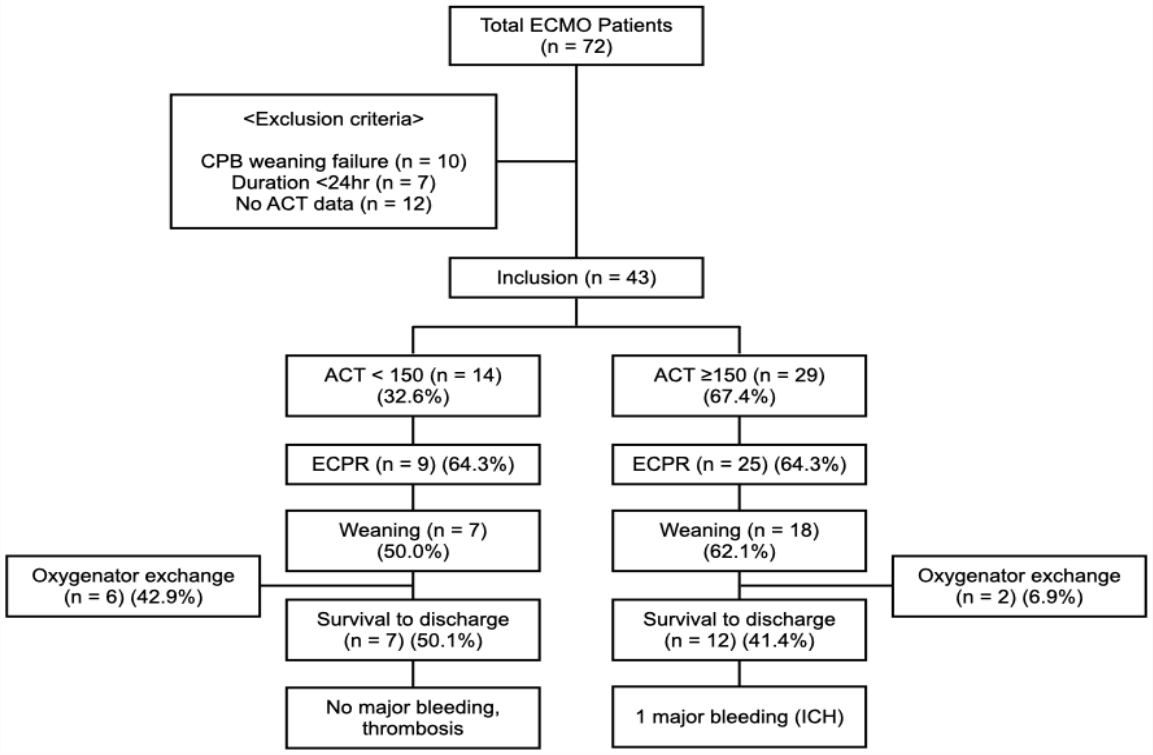

Figure 1: Flow chart showing the inclusion and exclusion criteria for the study population.
ACT: Activated Clotting Time; CPB: Cardiopulmonary Bypass; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardiopulmonary Resuscitation

n=12; Figure 1).

Cannula size was chosen according to the weight of the patient and diameter of vessels by ultrasound measurement. The venous cannula were inserted into the common femoral vein or the internal jugular vein and the arterial cannula was inserted into the common femoral artery, depending on the type of ECMO. The 19 Fr-23 Fr venous (draining) and 17 Fr to 19 Fr (Medtronic, MN) perfusion (outflow) cannula were used. During VV ECMO, the tip of the draining catheter was placed in the inferior vena cava and the tip of the perfusion cannula was placed in the right atrium through the femoral vein or the right internal jugular vein. The position of the cannula was adjusted to minimize re-circulation. During VA ECMO, the draining cannula was placed in the inferior vena-cava through the femoral vein and the perfusion cannula was placed in the femoral artery. Percutaneous Seldinger technique- with or without ultrasound guidance- was the preferred method. Lower leg perfusion through a distal-perfusion catheter was routinely performed at the bedside.

We used two different sets of ECMO circuits as follows: One circuit comprising a poly-methyl-pentene membrane oxygenator (PLS Quadrox, Maquet Cardiopulmonary, Hirrlingen, Germany), a centrifugal pump (Rotaflow, Maquet Cardiopulmonary, Hirrlingen, Germany), and recombinant human albumin and heparin-coated tubes (Bioline, Maquet Cardiopulmonary, Hirrlingen, Germany) and the other circuit comprising a poly-methyl-pentene membrane oxygenator (Terumo CAPIOX EBS, Japan), a centrifugal pump (SL 45, Terumo CAPIOX EBS, Japan), and biocompatible hydrophilic polymer surface coated tubes (Xcoating, Terumo, Japan).

During cannulation, a heparin bolus (30 to 50 units/kg body weight) was administered at the discretion of the attending clinician. The ACT was measured at the bedside using a portable Hemochron 401 device (Hemochron, ITC Medical, Edison, NJ, USA) with HRFTCA510 tubes. After ECMO, the ACT was measured to be in the guideline range of 180 sec to 220 sec. The circuit was then managed either without heparin or with low-dose continuous intravenous UFH. If the ACT was >200 s due to Cardiopulmonary Resuscitation (CPR) -related hypothermia, deteriorating coagulopathy, or previous intake of antiplatelet medications, like ticagrelor, and cannulation site bleeding, mucosal bleeding, or bloody nasogastric tube drains developed, UFH infusion was not initiated until the resolution of the aforementioned conditions. A low ACT was maintained unless the oxygenator showed a visual clot; left ventricular thrombus or spontaneous echo contrast was observed on echocardiography. An ACT point-of-care test was performed every hour until stabilization, and then the interval was increased to every 2 h to 4 h. Besides the ACT, laboratory measures, such as aPTT (measured every 6 h) and fibrinogen, d-dimer, and antithrombin III levels were also monitored on a daily basis. We did not routinely perform thromboelastography or anti-factor Xa assay. If the patient developed bleeding complications despite maintaining low ACT levels, anticoagulation therapy was stopped. To resume anticoagulation therapy, either bleeding complications should resolve or the risk of thrombosis should outweigh the hemorrhagic conditions. The circuit was routinely checked for any visible clot formation. Plasma-free hemoglobin levels were monitored and post-oxygenator blood gas analysis was performed to assess the efficacy of the oxygenator. The oxygenator was changed if inadequate post-oxygenation blood gas analyses results were obtained or gross hematuria or clot larger than 5 mm at infusion side of circuit was detected in the oxygenator. The target ACT range varied according to the patient's condition and

the clinician's preference (ACT goal 130 s-200 s). There is no agreed protocol among clinicians regarding anticoagulation management during bleeding incidents. In the corresponding author's case, heparin infusion was stopped when bleeding occurred, and the ACT level was checked every hour until it reached below 130 s. When ACT reached ≤ 130 s, heparin infusion was reinitiated at a rate of 5 unit/kg with careful observation of signs of rebleeding such as a low-volume state causing catheter lines to swing or hypotension. The ACT level was usually between 140 and 150 s in these patients. The patients were divided into two groups, namely, the low ACT or conventional ACT groups, according to a cut-off ACT of 150 s for comparison. We used the median ACT observed on ECMO day 2 when the intravenous UFH dose had been titrated and ACT stabilized in the desired range. The blood products were transfused to reach a target hemoglobin concentration >9.0 g/dl, platelet count >50,000/mm^3, International Normalized Ratio (INR) <1.5, and fibrinogen concentration >200 mg/dl. The whole procedure from ECMO cannulation to weaning was performed and supervised by three cardiothoracic surgeons and a perfusionist. The primary outcomes were thromboembolism and bleeding event, and the secondary outcomes were the rate of successful weaning from ECMO support and survival to discharge.

Statistical analysis

Continuous variables are expressed as median and range or mean and standard deviation. The descriptive statistics are expressed as count and percentage. The chi-square test or Fisher's exact test was used to compare the categorical variables. The Student's t-test or Mann-Whitney U-test was used to compare the continuous variables. Univariate and multivariate logistic regression analyses were used to identify the risk factors for successful weaning from ECMO support and survival to discharge. The results were considered statistically significant if the p-value was <0.05. SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

A total of 72 ECMO procedures were performed from March 2017 to October 2019. There were 14 patients with ACT <150 s (low ACT group) and 29 patients with ACT ≥ 150 s (conventional ACT group). In the low ACT and the high ACT group, the mean ACT was 139.8 ± 6.8 s and 181.4 ± 22.6 s, respectively (p=0.001) (Figure 2).

There were no significant differences in the baseline characteristics of the two groups before ECMO (Table 1). There was a dominance of male patients in each group. The comorbidities included dyslipidemia (most common), hypertension, diabetes mellitus, chronic kidney disease, history of Percutaneous Coronary Intervention (PCI), and history of Cerebrovascular Accident (CVA).

Table 2 shows the ECMO components in each group. The VA and VV ECMO rates did not differ in the low ACT and conventional ACT groups (9:5 *vs.* 22:7, p=0.428). The proportion of patients receiving Extracorporeal Cardiopulmonary Resuscitation (ECPR) in the low ACT and conventional ACT groups was 64.3% (n=9) and 86.2% (n=25), respectively (p=0.098). The frequency of use of the PLS and EBS machines was similar between the low ACT and conventional ACT groups (7:7 *vs.* 14:15, p=0.916). The duration of ECMO support in the low ACT and conventional ACT groups was 17.5 ± 7.7 days and 20.7 ± 5.6 days, respectively (p=0.102). The average flow rates were also similar between the low ACT and conventional ACT groups (2.7 ± 1.3 *vs.* 2.9 ± 1.1 L/min, p=0.819).

Of the 14 patients in the low ACT group, 7 (50%) patients were weaned-off from ECMO support, and all patients survived until discharge without further complications. Of the 29 patients in the conventional ACT group, 18 (62.1%) patients were successfully weaned-off from ECMO support. However, 12 (41.4%) patients survived until discharge. The cause of death was septic shock (n=5) and intracranial hemorrhage (ICH; n=1). All of the patients in low and conventional ACT group who weaned off from ECMO successfully had their heart function restored to a level where it could be managed adequately with medical management without heart transplants. There was no significant difference in the weaning rate (p=0.452) and survival to discharge rate (p=0.594) between the two groups. However, it could imply a meaningful difference in studies with larger sample sizes.

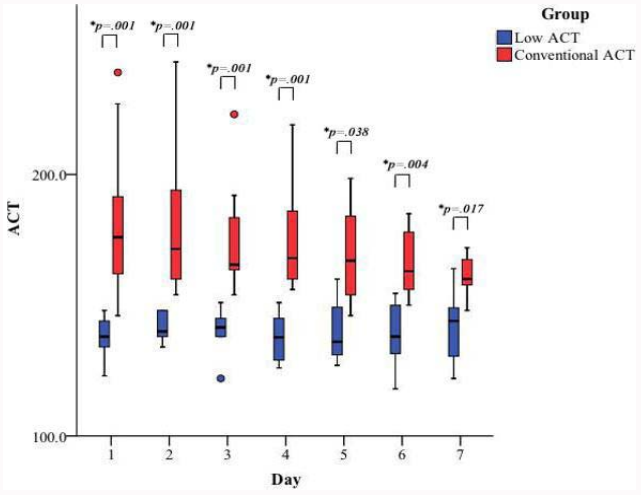

Figure 2: Difference in the mean ACT between the low ACT and conventional ACT groups from ECMO day 1 to 7.
ACT: Activated Clotting Time; ECMO; Extracorporeal Membrane Oxygenation

Of the 9 patients receiving ECPR in the low ACT group, 6 (66.6%) ECPR were weaned-off from ECMO support uneventfully, and all patients survived until discharge. Among the 25 patients receiving ECPR in the conventional ACT group, 16 (64.0%) patients were successfully weaned-off but only 10 (40.0%) patients survived until discharge. There was no significant difference in the weaning rate (p=0.866) and the survival to discharge rate (0.169; Table 3).

The ECMO-related complications, such as oxygen exchange rate, intra-circuit clot formation, and cannulation site bleeding

Table 1: Baseline characteristics of the two groups before ECMO.

	Low ACT (n=14)	Conventional ACT (n=29)	P-value
Age (years)	59.6 ± 10.4	57.2 ± 16.2	0.611
Male (n)	8 (57.1%)	18 (62.1%)	0.757
Comorbidities (n)			
Hypertension	9 (64.2%)	12 (41.4%)	0.159
DM	3 (21.4%)	12 (41.4%)	0.198
CKD	1 (7.1%)	2 (6.9%)	0.976
Dyslipidemia	9 (64.3%)	15 (51.7%)	0.437
h/o PCI	3 (21.4%)	7 (24.1%)	0.844
h/o CVA	3 (21.4%)	5 (17.2%)	0.741

ACT: Activated Clotting Time; CKD: Chronic Kidney Disease; CVA: Cerebral Vascular Accident; DM: Diabetes Mellitus; ECMO: Extracorporeal Membrane Oxygenation; PCI: Percutaneous Coronary Intervention

Table 2: ECMO-related components of the two groups.

Variables	Low ACT (n = 14)	Conventional ACT (n=29)	P-value
ECMO type (VA/VV) (%)	9 (64.3)/5 (35.7)	22 (75.9)/7 (24.1)	0.428
ECPR (%)	9 (64.3)	25 (86.2)	0.098
ECMO duration (days)	17.5 ± 7.7	20.7 ± 5.6	0.102
ECMO machine (PLS/EBS) (%)	7 (50.0)/7 (50.0)	14 (48.3)/15 (51.7)	0.916
Average flow rate (L/min)	2.7 ± 1.3	2.9 ± 1.1	0.819
Initial ACT (s)	176.0 ± 52.0	202.8 ± 65.9	0.19
Mean ACT (s)	139.8 ± 6.8	181.4 ± 22.6	0.001
Successful weaning (%)	7 (50.0)	18 (62.1)	0.452
Survival to discharge (%)	7 (50.0)	12 (41.4)	0.594
ECMO-related complications			
Oxygenator exchange	6	2	0.009
Circuit clot	1	0	0.145
Cannulation site bleeding	1	0	0.145
Oral cavity bleeding	0	1	0.145
Intracranial hemorrhage	0	1	0.482

ACT: Activated Clotting Time; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardiopulmonary Resuscitation; VA: Veno-Arterial; VV: Veno-Venous

Table 3: Comparison of the ECMO weaning and survival rates among the patients receiving ECPR between the two groups.

	Low ACT (n=9)	Conventional ACT (n=25)	P-value
Successful weaning (%)	6 (66.6)	16 (64.0)	0.866
Survival to discharge (%)	6 (66.6)	10 (40.0)	0.169

ACT: Activated Clotting Time; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardiopulmonary Resuscitation

or hematoma, gastrointestinal bleeding, and cerebrovascular accident (either ischemic or hemorrhagic) events, were assessed. The oxygenator exchange rate was significantly higher in the low ACT group than in the conventional ACT group (6 patients *vs.* 2 patients, p=0.009). Five oxygenators were electively replaced due to the oxygenator's decreased oxygen exchange capability, and one was replaced due to a clot visible inside the circuit without change in the ECMO flow. Bleeding occurred in 3 patients in the conventional ACT group (previous heel wound, n=1; oral cavity, n=1; ICH, n=1) and in 1 patient in the low ACT group (femoral artery cannulation site) who was permitted voluntary movement before heart transplantation 19 days after ECMO.

Discussion

Optimal anticoagulation is critical for successful ECMO support. To the best of our knowledge, there are no randomized controlled studies on adequate anticoagulation strategies in patients at a high risk of bleeding during ECMO. Improvements in the ECMO equipment, including centrifugal pumps, poly-methyl-pentene membrane oxygenators, and heparin-coated circuits aid in reducing the incidence of thrombosis during and after heparin discontinuation. With these improvements, systemic heparinization during ECMO may be reduced or stopped and the use of subcutaneous low molecular weight heparin (enoxaparin 40 mg/day to 80 mg/day) may be feasible [4-9].

According to the Extracorporeal Life Support Organization (ELSO) guidelines, the therapeutic anticoagulation range is defined as an ACT of 180 s to 220 s. This is, however, not universally agreed upon. The guidelines suggest decreasing the anticoagulant infusion rate until the ACT is 1.4 to 1.5 times the normal range while managing bleeding during ECMO support [2]. The lack of clarity in the guidelines encourages the clinicians to refrain from maintaining relatively higher ACT in patients with minor or major bleeding. According to a recent international survey, the target ACT for VA and VV ECMO ranged from 140 s to 220 s. The majority of the institutions used an ACT between 160 s and 200 s [3].

In this study, we report the safety and efficacy of a lower ACT in patients on ECMO support. The rate of weaning from ECMO support and survival to discharge did not show a significant difference between the low and conventional ACT groups. All patients in the low ACT group and two-thirds of the patients in the high ACT group who were successfully weaned from ECMO support were discharged to home. A majority of the patients who did not survive after weaning died from septic shock. A patient in the high ACT group developed ICH during ECMO and died, despite being successfully weaned from ECMO support even after normalization of the coagulation status. Another patient with diabetes mellitus in the high ACT group had bleeding from the heel of the foot, which required electro-cauterization. In the low ACT group, no major thromboembolic event, such as stroke, pulmonary thromboembolism, or mesenteric ischemia was observed. A patient in the low ACT group developed cannulation site bleeding after 7 days of ECMO support. This patient was allowed awakening without mechanical ventilation and the arterial cannula site bleeding occurred while moving in bed. The bleeding finally stopped after heart transplantation and ECMO support was terminated after 19 days.

The oxygenator exchange rate was significantly higher in the low ACT group. Six patients required oxygenator replacement. A grossly visible clot formed inside the VV-ECMO circuit in one patient. In the remaining 5 patients, there was decreased oxygenation capability on post-oxygenator blood gas analysis. This may be due to the formation of microthrombi that affect the fibers of the oxygenator membrane.

As mentioned above, the heparin-coated circuits allow decreasing or discontinuing the anticoagulation infusion for some time as long as the blood flow is maintained at a high rate. We believe that the

ECMO flow is also important to prevent thrombus formation in the oxygenator. In our study, the average flow rate was 2.7 ± 1.3 and 2.9 ± 1.1 L/min in the low ACT and high ACT groups, respectively, and was not significantly different (p=0.819). If the ECMO flow decreases for even <15 min, extensive thrombosis may develop in the four heart chambers, even when the ACT is high (>170 s) [10].

At our center, we try to maintain adequate left ventricular contraction and a wide range of pulse pressure to prevent intracardiac stagnation of blood and formation of thrombus. When pulse pressure range is narrow and there is echocardiographic evidence of severe left ventricular dysfunction without the opening of the aortic valve or spontaneous echogenic contrast in the left ventricle, we routinely perform left atrial vent using just 8-Fr Mullins sheath *via* the femoral vein [11-13]. There are an increasing number of reports on maintaining low ACT during ECMO [4-9]. However, except for two studies, most studies focus on VV ECMO related to multiple trauma and ICH [4-6,8].

The concept of maintaining ECMO in cases of multiple trauma with severe bleeding and ICH with heparin-free or heparin-sparing strategy is evolving [4,5,14,15]. This concept is being accepted by most intensivists presently. However, there are only a few reports on the feasibility of low ACT during VA ECMO [7,9]. ECPR is usually associated with hypothermia, metabolic acidosis-induced coagulopathy, and anti-platelet medication, like clopidogrel or ticagrelor-induced platelet dysfunction before PCI, and mechanical chest wall massage-induced bleeding, like sternal or rib fracture or intra-pericardial bleeding. Sometimes, it is accompanied with cannulation site and mucosal bleeding and bloody nasogastric tube drains. We maintained a lower ACT during ECPR than during ECMO due to the higher tendency for bleeding. When initiating ECPR, we usually administer a heparin bolus (30 units/kg to 40 units/kg) and check the ACT every hour until it reaches ~140 s before continuous intravenous infusion of heparin is initiated. If the bleeding persists and there is unstable ECMO flow, we usually do not initiate heparin infusion even when ACT is ~120 s to 130 s. After bleeding is stopped, we initiate intravenous heparin with caution to prevent re-bleeding. Compared with other studies [4-9,12,15], our study did not include multiple trauma patients on VV ECMO support. In the low ACT group, all VA ECMO support was with ECPR. ECMO component exchange due to clotting can be quickly performed when the ICU team is well-trained; however, major bleeding is harmful and difficult to treat [8]. In our series, oxygenator exchange was more common in the low ACT group but the incidence of serious bleeding and thrombosis was not observed more commonly. Although we could not identify any risk factor for ECMO weaning, dyslipidemia was a risk factor for survival to discharge. A low ACT was not a risk factor for weaning and survival.

This study has several limitations. First, this is a retrospective analysis of a relatively small sample population at a single center. Second, the oxygenator and cannula thrombus formation was assessed by gross inspection of the oxygenator from the outside, and microthrombi that did not influence oxygenator function may be present. Third, we did not compare other anticoagulation monitoring methods, like analysis of the aPTT, thromboelastography and anti-factor Xa assay.

Conclusion

A lower target ACT (<150 sec) was not associated with an increased thromboembolic risk, weaning failure, and mortality during ECMO management. A lower ACT may be considered for patients with ongoing bleeding or who are at a high risk of hemorrhagic complications. Further randomized controlled and multicenter studies are required to validate our study results.

Author Contributions

Jeong In Hong wrote draft. Jinwook Hwang reviewed draft. Hong Ju Shin wrote final manuscript.

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