The Heart Surgery Forum #2019-2645
22 (5), 2019 [Epub September 2019]
doi: 10.1532/hsf.2645

Online address: http://journal.hsforum.com

Novel Approach of Antithrombotic Potency Amongst Patients Admitted to Hospital with Bleeding Using HEMORR2HAGES Score: A Retrospective Cohort Study

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ABSTRACT

Background: The purpose of this study was to evaluate whether a relationship exists between baseline HEMORR$_2$HAGES score and antithrombotic potency amongst patients presenting with bleeding complication. We hypothesized that the more antithrombotic regimen potency, the less HEMORR$_2$HAGES score you have.

Methods: This is a retrospective observational study of patients admitted with a diagnosis of active bleeding between November 1, 2013 and August 31, 2015. The antithrombotic groups included patients on the following regimens: single antiplatelet therapy (SAP), single oral anticoagulant therapy (SOAC), dual antiplatelet therapy (DAPT), dual combination (SOAC+SAP), and triple antithrombotic therapy. The primary outcome was to review the mean HEMORR$_2$HAGES score among the various groups.

Results: There were a total of 180 patients in the study. No significant difference was noted among the five groups in the HEMORR$_2$HAGES score (P = .36). The highest HEMORR$_2$HAGES score was in the SAP group (3.23 ± 1.1). The lowest HEMORR$_2$HAGES score was in the DAPT group (2.59 ± 1.2). In the Sub Group analysis, we compared single versus dual versus triple therapy, and we found the lowest HEMORR$_2$HAGES score in the triple therapy group (2.70 ± 1.6); (P = .29).

Conclusions: Among patients admitted with active bleeding, the HEMORR$_2$HAGES score did not differentiate antithrombotic potency amongst groups with various regimens. This study highlights the necessity to evaluate antithrombotic therapy according to benefits and harms.

INTRODUCTION

Background: There has been a marked increase in the number of antithrombotic therapies to treat patients with cardiovascular and thromboembolic events. With the increased use of several antithrombotic therapies, complications such as bleeding may result in significant morbidity [Lamberts 2012]. Current evidence supports the use of dual antiplatelet therapy after percutaneous coronary intervention (PCI) to reduce the risk of stent thrombosis or acute coronary syndrome (ACS), and the use of oral anticoagulants (OACs) to prevent cardioembolic neurologic events in patients with atrial fibrillation (AF) [D'Ascenzo 2013]. The use of OACs and dual-antiplatelet therapy (DAPT) is believed to increase the risk of fatal and nonfatal bleeding by retrospective analysis [Gage 2006]. The rate of bleeding is expected to be more frequent with the use of triple therapy (DAPT + OAC) from recent studies [Orford 2004; Andrade 2013; Hansen 2010; Sorensen 2009; Rubboli 2008]. To decrease the risk of bleeding with the use of antithrombotic therapy, the recent 2019 guideline for the management of atrial fibrillation considered the reduction of the duration of triple therapy to a period of 4-6 weeks

Table 1. Definition of HEMORR2HAGES score

HEMORR2HAGES Risk Factors	Definition
Hepatic (1) or Renal Disease (1)	Cirrhosis; >two-fold AST or ALT; Crcl <30 mL/min
Ethanol use (1)	Alcohol abuse, recent hospitalization for alcoholism
Malignancy (1)	Recent metastatic cancer
Older (age >75) (1)	Calculated from birth date
Reduced platelet count (1)	Platelets <75,000
Re-Bleeding (2)	Prior hospitalization bleeding
Hypertension, uncontrolled (1)	BP not in control; Systolic BP ≥ 160 mmHg
Anemia (1)	Hematocrit <30 g/dL or Hemoglobin <10 g/dL
Genetic factors (1)	CYP2C9*2 and/or CYP2C9*3
Elevated risk of fall (1)	Alzheimer, dementia, Parkinson's, or schizophrenia
Stroke (1)	Prior ischemic stroke or brain infraction

AST = aspartate aminotransferase; ALT = alanine aminotransferase; Crcl = creatinine clearance; BP = blood pressure; CYP = cytochrome P450 enzyme

Received June 30, 2019; accepted August 5, 2019.

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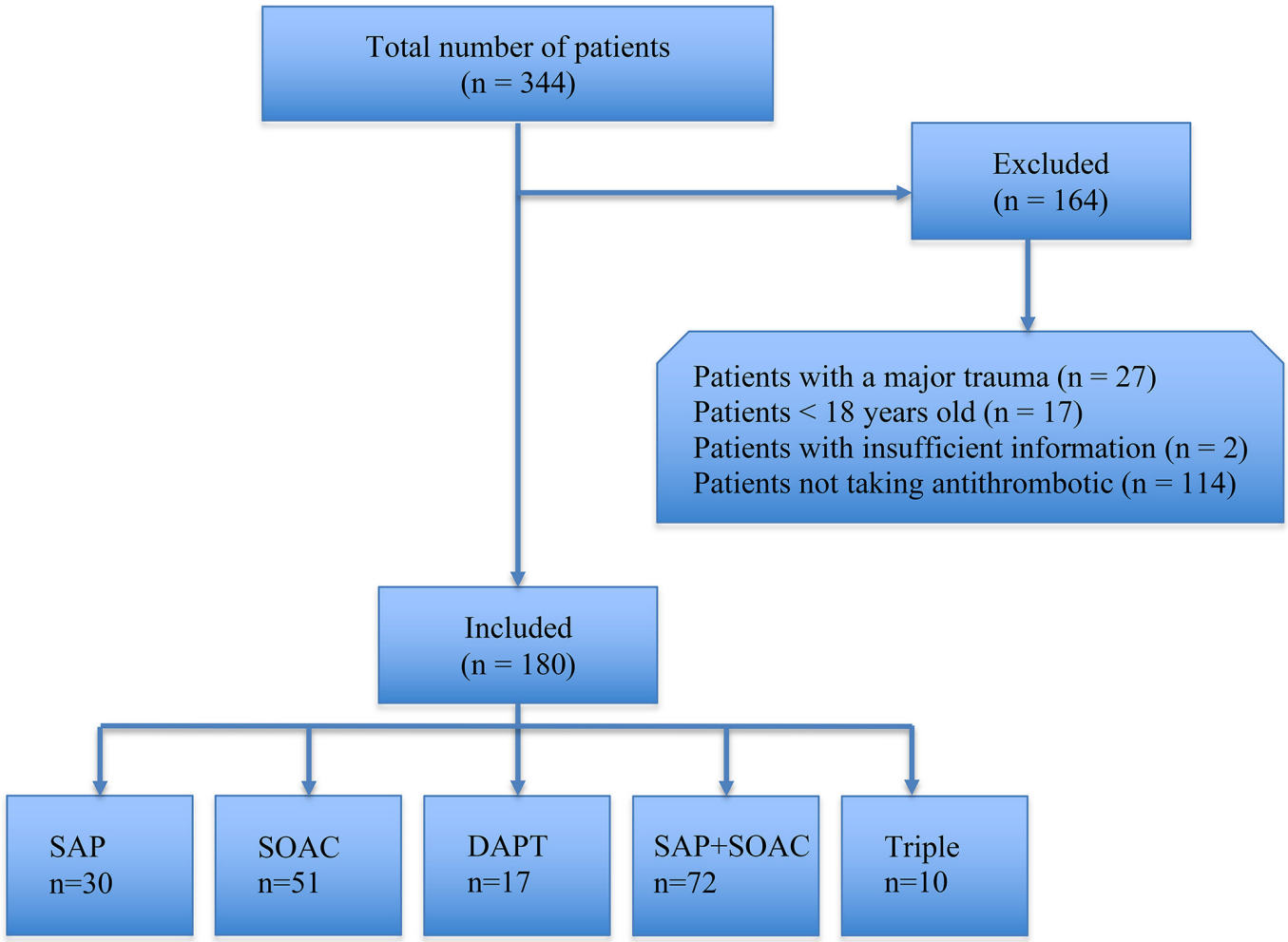

Flow of patients through the study

for patients with ACS and AF who are at high risk of stroke [January 2019]. Appropriate management of these patients still is the source of much debate [Zhao 2011].

The optimal treatment of AF patients with the need for life-long anticoagulation or antiplatelet therapy is evolving. Clinical trials evaluating the safest combinations are lacking, and the appropriate management of those populations is still challenging and a burden to many practitioners [Hansen 2010; Sorensen 2009; Rubboli 2008]. With the introduction of novel oral anticoagulants (NOACs) and new antiplatelet agents, the question regarding the ideal combination will continue to be raised, and the risk of bleeding accompanied with each regimen will be uncertain. Bleeding risk with triple therapies that include NOACs is unknown and a direct comparison of bleeding risk has not been made involving many newer regimens of anticoagulant drug combinations.

Guidelines recommend the assessment of stroke and bleeding risk before initiating anticoagulation in patients with AF and other cardiovascular diseases [Kearon 2012; Konstantinides 2014]. Multiple scoring systems have been proposed to predict the risk of major bleeding in AF populations, including the HEMORR$_2$HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older age, Reduced Platelet Count or Function, Re- Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke) [Gage 2006]; HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) [Pisters 2010]; and ATRIA (Anticoagulation and Risk factors in Atrial Fibrillation) [Fang 2011]. These act as validated scores in estimating the incidence of relevant bleeding in different patient populations [Apostolakis 2012; Klolk 2016].

The HEMORR$_2$HAGES score consists of eleven criteria, including Hepatic or renal disease, Ethanol abuse, Malignancy, age > 75 years, Reduced platelet count or function, Re-bleeding risk, uncontrolled Hypertension, Anemia, Genetic factors, Excessive fall risk, and Stroke. Each bleeding risk factor weighs 1 point, except for a prior bleed, which weighs 2 points (R in the mnemonic). The rate of bleeding increases markedly with the higher score [Gage 2006] (see Table 1).

The HEMORR$_2$HAGES score could be a good indicator for the estimation of bleeding risk in a number of antithrombotic medications, such as NOACs, whereas HAS-BLED might be more directed to warfarin [Gage 2006; Apostolakis

Table 2. Baseline Characteristics

Variable	SAP N = 30	SOAC N = 51	DAPT N = 17	SAP+SOAC N = 72	Triple N = 10	*P*
Age, mean (SD)	69.9 (19.4)	62.9 (17.6)	69.4 (13.9)	71.9 (12.9)	78.6 (4.8)	.0076
Male, N (%)	20 (66.7%)	26 (50.9%)	10 (58.8%)	44 (61.1%)	7 (70.0%)	.55
Weight (kg), mean (SD)	72 (14)	77 (12)	73 (20)	80 (13)	70 (11)	.40
Height (cm), mean (SD)	173 (12)	173 (10)	171 (14)	179 (14)	177 (16)	.60
Serum creatinine, (mg/dL), mean (SD)	1.1 (0.3)	1.0 (0.5)	1.2 (0.4)	1.3 (0.2)	1.4 (0.3)	.70
Creatinine clearance (mL/min), mean (SD)	51 (14)	54 (16)	49 (14)	44 (18)	41 (13)	.43

SAP = single antiplatelet; SOAC = single oral anticoagulant; DAPT = dual antiplatelet; SAP+SOAC = combination of single antiplatelet and single oral anticoagulant; N = number; SD = standard deviation

2012; Klolk 2016; Zalesak 2013]. According to our knowledge, no studies have evaluated the HEMORR$_2$HAGES score for patients on DAPT and triple therapy, which makes this study a good start for considering this score in the future with a larger sample size.

Goal of this investigation: We hypothesized that the more antithrombotic regimen potency, the less HEMORR$_2$HAGES score you have. The primary objective of our study is to examine whether a relationship exists between a baseline HEMORR$_2$HAGES score and antithrombotic potency among patients presenting with a bleeding complication by calculating the HEMORR$_2$HAGES score among different regimens.

METHODS

Study design: This study was a retrospective observational study between November 1, 2013 and August 31, 2015. It was conducted at Banner University Medical Center Tucson (BUMCT) in Tucson, AZ, USA, a 479-bed teaching medical center. The study received institutional review board approval, according to the institution's policy.

Selection of participants: The study enrolled patients admitted to hospital with a diagnosis of bleeding. Patients were included in our study based on an International Classification of Disease, Ninth Revision (ICD-9 code) of 578.0, 578.1, 578.9, 432.1, 386.30, 386.31, 386.39, 459.0, and 853.0 indicating a diagnosis of active bleeding not limited to: intracranial hemorrhage, subdural hematoma, GI bleeding, melena, hemoptysis, hematemesis, retroperitoneal bleeding, or fatal bleeding.

Subjects were eligible in our study if they: (1) were age 18 years or older, and (2) had confirmed active bleeding diagnosis. Subjects were excluded if they: (1) had a major trauma, (2) were not taking antithrombotic medications, and (3) had insufficient information to perform a retrospective review.

The antithrombotic groups in our study included patients who were on the following regimens: single antiplatelet therapy (SAP), single oral anticoagulant therapy (SOAC), dual antiplatelet therapy (DAPT), dual combination (SOAC+SAP), and triple antithrombotic therapy.

In the Sub Group analysis, we ended up combining patients on SAP and SOAC, who were on single antithrombotic therapy, into a new modified Group 1, and combined patients on DAPT and SAP+SOAC, who were on two antithrombotic therapies, into a new modified Group 2 and kept those patients who were on triple therapy.

Data collection – Outcomes: The following information was collected in our study, including but not limited to demographic data, serum creatinine, estimated creatinine clearance using Cockcroft-Gault Equation, name and dose of antithrombotic therapy, appropriateness of antithrombotic medications based on renal dosing for NOACs and INR for warfarin, and total HEMORR$_2$HAGES score. This was based on concomitant disease states, including hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, re-bleeding risk, hypertension (uncontrolled), anemia, genetic factors (CYP 2C9 single nucleotide polymorphisms), excessive fall risk (including neuropsychiatric disease), and stroke (Table 1). To improve our consistency toward the calculated score, we added one point for each patient who had a history of uncontrolled hypertension defined as systolic BP ≥ 160 mmHg, from at the time of admission to our facility or during any point in the patient's hospitalization.

The primary outcome of this study was to calculate the mean HEMORR$_2$HAGES score among various antithrombotic regimens.

Data analysis: Categorical variables were evaluated by using a chi-square analysis unless the sample size for a case was less than 5, and in those cases, a Fisher's exact test was used. Normally distributed continuous variables were analyzed by using ANOVA test, and Bonferroni correction test was used for post hock analysis when the difference exists.

RESULTS

Of the 344 patients identified, 180 patients met the inclusion criteria. Of those, 30 were in the SAP Group, 51 were in the SOAC Group, 17 were in the DAPT Group, 72 were in the dual combination of SAP+SOAC Group, and 10 were in the Triple Therapy Group. Of the 164 patients excluded, 114 were not

Table 3. Outcomes

Variable	SAP N = 30	SOAC N = 51	DAPT N = 17	SAP+SOAC N = 72	Triple N = 10	*P*
Hepatic/Renal, N (%)	7 (23.3%)	10 (19.6%)	3 (17.7%)	14 (19.4%)	1 (10.0%)	.93
Ethanol abuse, N (%)	2 (6.7%)	5 (9.8%)	0 (0.0%)	2 (2.8%)	0 (0.0%)	.30
Malignancy, N (%)	8 (26.7%)	12 (23.5%)	3 (17.7%)	10 (13.9%)	0 (0.0%)	.24
Age >75 years, N (%)	13 (43.3%)	10 (19.6%)	7 (41.2%)	36 (50.0%)	7 (70.0%)	.003
Reduced platelet, N (%)	2 (6.7%)	10 (19.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	.0003
Re-bleeding, N (%)	7 (23.3%)	18 (35.3%)	3 (17.7%)	11 (15.3%)	3 (30.0%)	.12
Hypertension, N (%)	24 (80.0%)	31 (60.8%)	16(94.1%)	67 (93.1%)	10 (100%)	<.001
Anemia, N (%)	17 (56.7%)	31 (60.8%)	7 (41.2%)	43 (59.7%)	2 (20.0%)	.11
Fall, N (%)	3 (10.0%)	2 (3.9%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	.20
Stroke, N (%)	7 (23.3%)	4 (7.8%)	3 (17.7%)	11 (15.3%)	1 (10.0%)	.39
$HEMORR_2HAGES$ score, mean (SD)	3.23 (1.1)	2.96 (1.2)	2.59 (1.2)	2.86 (1.0)	2.70 (1.6)	.36

SAP = single antiplatelet; SOAC = single oral anticoagulant; DAPT = dual antiplatelet; SAP+SOAC = combination of single antiplatelet and single oral anticoagulant; N = number; SD = standard deviation

on antithrombotic therapy, 27 had trauma, 17 were less than 18 years old, and 5 had insufficient information (Figure).

Overall, patients on SOAC therapy significantly were younger than the other groups. The mean age (± SD) was (62.9 ± 16.7 years; $P = .0076$) (Table 2). Patients with a history of hypertension significantly were less represented in the SOAC Group compared with the other groups (60.8 %; $P \leq .0001$) (Table 3). The most common antiplatelet used in this study was aspirin (68.9%), followed by clopidogrel (14.4%) and ticagrelor (3.3 %). We did not have any patients taking prasugrel in our study. The most common anticoagulant used was warfarin (39.9%), followed by rivaroxaban (23.9%), followed by dabigatran (7.8%), and apixaban (2.8%). We had only one patient on edoxaban (0.6%). The most frequently used combination for DAPT was aspirin and clopidogrel (82.4%). The most common triple antithrombotic therapy was aspirin, clopidogrel, and dabigatran (30%). Finally, we found that (83.9%) of our subjects received appropriate dosing of the antithrombotic therapy, including therapeutic INR at the time of bleeding.

There was no significant difference among the five groups in the following disease states: history of hepatic or renal disease, ethanol abuse, history of rebleeding, history of fall, and history of stroke. We found a significant difference between the SAP and SOAC groups in the history of reduced platelet count or function 6.7% versus 19.6%; $P = .0003$. Also, there was a significant difference in patients older than 75 years between the SOAC and dual combination SAP+SOAC groups 19.6% versus 41.2% and between the SOAC and Triple Therapy groups 19.6% versus 70%; $P = .003$. In addition, patients with a history of hypertension significantly were less represented in the SOAC Group compared with the other groups; $P \leq .0001$ (see Table 3).

Main Results

The $HEMORR_2HAGES$ score was highest in the SAP Group compared with the other groups (3.23 ± 1.1). Interestingly, patients in the DAPT Group had the lowest $HEMORR_2HAGES$ score compared with the other groups (2.59 ± 1.2). However, there was no significant difference among all the groups in the $HEMORR_2HAGES$ score ($P = .36$) (see Table 3).

In the Sub Group analysis, we found that the $HEMORR_2HAGES$ score was highest in the modified Group 1 compared with the modified Group 2 and Triple Group, 3.06 ± 1.1 versus 2.80 ± 1.1 versus 2.70 ± 1.6, respectively; $P = .29$. We found a trend of decreasing the mean $HEMORR_2HAGES$ score as we added more antithrombotic therapy; however, there still was no statistical difference among the three groups (see Table 4).

DISCUSSION

The ideal combination of treatments in patients with atrial fibrillation and coronary artery disease remains unclear due to lack of a head-to-head trail among the new agents; therefore, it is important to understand the associated outcomes of these various agents [Hansen 2010; Sorensen 2009; Rubboli 2008; Kearon 2012; Konstantinides 2014]. Since the major concern with initiating all antithrombotic agents is the high risk of bleeding, the availability of various bleeding risk score can be crucial in determining whether the benefits outweigh the risks.

$HEMORR_2HAGES$ bleeding score originally was developed from the results of the National Registry of Atrial Fibrillation (NRAF) to quantify the risk of bleeding in elderly patients with atrial fibrillation. In its study, the mean $HEMORR_2HAGES$ score was 1.9 for warfarin group, 3.1 for aspirin group ($P < .001$) [Gage 2006]. The results of NRAF highlighted the validity of using $HEMORR_2HAGES$ score as a good predictor of bleeding in patients who were prescribed warfarin or aspirin, but it

Table 4. Sub Group Analysis

Variable	Modified Group 1 SAP+SOAC N = 81	Modified Group 2 DAPT + (SAP+SOAC) N = 89	Group 3 Triple N = 10	*P*
HEMORR$_2$HAGES score, mean (SD)	3.06 (1.1)	2.80 (1.1)	2.70 (1.6)	.29

SAP = single antiplatelet; SOAC = single oral anticoagulant; DAPT = dual antiplatelet; SAP+SOAC = combination of single antiplatelet and single oral anticoagulant; N = number; SD = standard deviation

may be a valid score in patients prescribed newer anticoagulants as well [Gage 2006; Zalesak 2013].

According to our knowledge, there only was one study besides the NRAF to use the HEMORR$_2$HAGES score to examine persistence rate in newly diagnosed nonvalvular atrial fibrillation patients treated with warfarin versus dabigatran as their initial oral anticoagulation. The mean HEMORR$_2$HAGES score in this study was 2.4 ± 1.5 in warfarin group versus 2.7 ± 1.6 in dabigatran group; $P < .001$ [Zalesak 2013].

The mean HEMORR$_2$HAGES score in our study for both the SAP and SOAC groups was higher than what was reported in the two studies mentioned above [Gage 2006; Zalesak 2013]. One explanation is the inconsistency in reporting the different variables in the score, which may have affected some of the results. For example, history of uncontrolled hypertension (systolic BP ≥ 160 mmHg) could be considered at only the time of admission to our facility or at any point during patient's hospitalization. We ended up adding one point for any patient, of which 148 (82.2%), had any reading of systolic BP ≥ 160 mmHg during their entire admission to improve our consistency. At this point so far, we could not find any study that has measured the mean HEMORR$_2$HAGES score for patients on dual or triple antithrombotic therapy; therefore, we could not estimate the sample size for each group.

It is unclear why patients in the DAPT Group had the lowest HEMORR$_2$HAGES score in our study. The best explanation would be those 17 patients in the group were sicker than the other groups, though there were limited subjects in this group. We hypothesized that subjects in the Triple Therapy Group would have the lowest score since their risk of bleeding could be higher compared with one or two antithrombotic agents [Orford 2004; Andrade 2013; Hansen 2010; Sorensen 2009; Rubboli 2008]. This hypothesis was true in the Sub Group analysis, when we compared single versus dual versus triple therapy as Triple Therapy Group had the lowest score.

Individual elements of HEMORR$_2$HAGES score to predict bleeding showed difference in patients on SOAC therapy. This might be explained because the median age in the SOAC Group significantly was lower than the dual combination SOAC+SAP and Triple Therapy groups. In addition, patients with a history of hypertension and age >75 proportionately were less represented in the SOAC Group compared with other groups.

It should be noted that our study included patients with various thromboembolic diseases and did not only focus on atrial fibrillation patients. This concept allowed us to test the HEMORR$_2$HAGES score on several populations with different options of treatment. Thus, it helped us examine the function of this bleeding score with complicated regimens. However, there was no difference among the different groups mainly due to the low number of subjects in this study. The availability of a well-designed study with a larger population could be a promising idea for further testing of this bleeding score.

Several limitations should be considered in this study. First, we can't generalize the results of this study to all patients with active bleeding because we conducted this study in a single center. Second, the use of ICD-9 codes for the diagnosis of active bleeding in our institution might not capture all eligible patients. Third, we had a limited number of subjects in some of the antithrombotic regimens, which could affect the study power of our results. In addition, we could not find any prior study that had a controlled mean HEMORR$_2$HAGES score for different regimens as we used in our study. Finally, genetic risk factor for bleeding was not readily available in our study because this test was not available in our institution at the time that this study was conducted.

In conclusion, HEMORR$_2$HAGES score did not differentiate antithrombotic potency amongst groups with various regimens. This study emphasized that the decision to initiate antithrombotic therapy on patients at high risk of bleeding should always considered the harms and benefits.

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