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Safety and Efficacy of Routine Bridging Anticoagulation for Subtherapeutic Anticoagulation in Outpatients with a Left Ventricular Assist Device

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Abstract

Background

Anticoagulation with vitamin K antagonists is vital to prevent pump thrombosis in patients with left ventricular assist devices (LVADs). However, the safety and efficacy of bridging anticoagulation for the routine management of subtherapeutic international normalized ratio (INR) in stable outpatients remains poorly characterized.

Methods

In this retrospective study, a total of 60 LVAD outpatients had 110 episodes of subtherapeutic INR noted on routine testing. 34 of these episodes were managed with parenteral bridging anticoagulation and 76 were managed with only an adjusted dose of warfarin. The rates of bleeding and thromboembolic adverse events following these episodes of subtherapeutic INR were measured to evaluate the safety and efficacy of bridging anticoagulation in this population.

Results

Ischemic cerebrovascular events occurred following 2 bridged episodes compared to 4 non-bridged episodes (6% vs. 5%, p=0.895). Hemolysis occurred following 1

bridged episode compared to 3 non-bridged episodes (3% vs. 4%, p=0.794). Bleeding events occurred after 4 bridged episodes compared to 13 non-bridged episodes (12% vs. 17%, p=0.474). In a subgroup of patients with either a CHA2DS2-VASc score > 3 or a history of atrial fibrillation, thromboembolic events occurred only in those who did not receive bridging anticoagulation although this result was not statistically significant.

Conclusions

There was no benefit associated with the routine use of bridging anticoagulation in a general population of stable LVAD outpatients with subtherapeutic INR. A trend towards benefit was seen in a subset of patients with a CHA2DS2-VASc score of > 3 or a history of atrial fibrillation.

Keywords: left ventricular assist device, bridging, anticoagulation, bleeding, thrombotic complications

Introduction

The use of continuous-flow left ventricular assist devices (LVADs) has resulted in a significant improvement in survival and quality of life for patients with advanced heart failure.[1-3] However, this therapy continues to have a high burden of adverse events with frequent hospital readmissions due to bleeding, stroke, infection, and pump thrombosis.[4] Anticoagulation with vitamin K antagonists is a cornerstone of management for LVAD patients to prevent device thrombosis but is complicated by a need to maintain a therapeutic international normalized ratio (INR). The appropriate management of anticoagulation during periods when the INR is subtherapeutic is unclear. There is evidence that the use of parenteral bridging anticoagulation in the early post-implant course can help prevent pump thrombosis.[5] Current guidelines suggest that the use of heparin bridging may be considered for patients who need to be off of warfarin for procedures.[6] Despite frequent use, there is little data regarding bridging anticoagulation in LVAD outpatients with subtherapeutic INR, although a recent report suggested an increase in adverse events associated with bridging.[7] In the current study we investigate the efficacy and safety of bridging anticoagulation for the management of stable LVAD outpatients with subtherapeutic INR.

Methods

Patient Population

This is a retrospective study of LVAD (HeartMate II or HVAD) patients implanted at Jewish Hospital who utilize Alere (Alere Inc., Waltham, MA) home INR monitoring services and were noted to have a subtherapeutic INR on routine surveillance. Episodes of subtherapeutic INR were selected on the basis of INR measurements provided by Alere between April 1, 2015 and May 31, 2017. Alere home monitoring

was generally offered to all patients at our program, with enrollment largely dependent on insurance coverage and patient preference. The typical INR goal for our program was 2.0-3.0, but was often individualized based on either bleeding or thrombotic concerns. Routine INR checks were performed weekly for most patients, although testing frequency often changed at the discretion of the treatment team if an INR was out of range. For inclusion in the study, the patient's INR must have been 0.3 or more below the lower limit of their target INR range. This INR cutoff of 0.3 was based on a clinical practice protocol for bridging now used at our program based on physician consensus (created independently of this research study). We analyzed the data in this way both for research purposes and in an attempt to validate our clinical protocol. Subsequent episodes of subtherapeutic INR in the same patient were considered as separate episodes if they occurred at least 3 months after the preceding episode. Subtherapeutic episodes were only included if the patients were otherwise stable in the outpatient setting. Episodes in which the INR was subtherapeutic because warfarin was purposefully held for procedures or for other reasons were not included. Baseline patient characteristics and medical history were obtained via review of medical records.

The subtherapeutic episodes were then divided into bridged and non-bridged cohorts. Episodes were considered to have been bridged if the patient received at least one dose of parenteral anticoagulation (i.e. therapeutic enoxaparin or heparin) while the INR was subtherapeutic. The subsequent date at which the patient once again achieved therapeutic INR, and bridging was therefore stopped, was also noted. The decision to bridge or not bridge each episode was at the discretion of the supervising cardiologist at the time of the episode. The usual bridging dose was enoxaparin at 1 mg/kg twice daily, up to a maximum of 80 mg twice daily, until therapeutic INR was documented. Medical records were then reviewed to identify adverse events in the 3 months following the subtherapeutic episode. Relevant adverse events included bleeding events, thromboembolic events, and hospitalizations for any cause. A bleeding event was defined as hospitalization for clinical signs or symptoms of bleeding including new or worsening anemia. Intracranial bleeding was also classified as a bleeding event for this study. Thromboembolic events were defined as hemolysis (lactate dehydrogenase (LDH) greater than 2.5 times the upper limit of normal) or cerebrovascular (transient ischemic attack or ischemic stroke). In addition, the patients' baseline LDH values and as well as the maximum LDH in the 3 months following each subtherapeutic episode were recorded. A CHA2DS2-VASc, HAS-BLED, and ATRIA risk score was also calculated for each subtherapeutic patient episode based on the patient data available immediately prior to the episode. This research had institutional IRB approval.

Statistical Analysis

IBM SPSS (version 24.0, SPSS Corp, Chicago, IL, USA) was used for statistical analysis. Qualitative data is presented as frequencies and quantitative data as

mean ± standard deviation. Categorical variables were compared by using Chi-square test, and continuous variables were compared using Student's t-test. Significance was defined at p-value =<0.05.

Results

Patient and Episode Characteristics

A total of 70 LVAD patients with available Alere INR monitoring data were identified, which represented 67% of the 104 LVAD patients at our program during the study time. Of those patients, 60 had episodes of subtherapeutic INR meeting inclusion criteria. These 60 LVAD patients had 110 episodes of subtherapeutic INR that were identified for inclusion in the study. There were 9 patients, accounting for 30 subtherapeutic episodes, who had both bridged (11 episodes) and non-bridged (19 episodes) events. While the demographics data of these patients were included in both the bridged and non-bridged cohorts, removing these patients from analysis did not result in any meaningful differences in baseline group demographics (data not shown). The average patient was 61 ± 11 years old and 82% were male (Table 1). HeartMate II LVAD was present in 51% of patients and HVAD in 49%. Of the 110 subtherapeutic episodes, 34 (31%) were managed with bridging anticoagulation while the other 76 (69%) were managed with an increased dose of warfarin alone. All but one of the bridged episodes were treated with enoxaparin, with the remaining episode being treated with fondaparinux due to a history of heparin induced thrombocytopenia. The average lower target INR for both the bridged and non-bridged episodes was 2.0. The average presenting INR for bridged episodes was lower than that for non-bridged episodes (1.40 vs. 1.55, p=0.0001). The average number of days spent with subtherapeutic INR was 6.1 for bridged episodes versus 9.5 for non-bridged episodes (p=0.008) (Table 1).

Outcomes

Within 3 months of the subtherapeutic episode 17 of the patients who received bridging anticoagulation were subsequently hospitalized for any reason compared to 31 of those who were not bridged (50% vs. 41%, respectively, p=0.368) (Table 2). Bleeding events occurred in 4 of the bridged patients compared to 13 of the non-bridged patients (12% vs. 17%, p=0.474). One of these bleeding events was an intracerebral hemorrhage that ultimately resulted in death, which occurred 61 days after an episode of subtherapeutic INR in a patient that was bridged with enoxaparin based on a presenting INR of 1.2. This was the only death noted to have occurred within 3 months of a suptherapeutic INR episode during this study. Of the remaining bleeding events, 12 were for clinically apparent gastrointestinal bleeding, 2 for anemia of unclear etiology, 1 for epistaxis, and 1 for bleeding at the driveline exit site. Ischemic cerebrovascular events occurred following 2 bridged episodes compared to 4 non-bridged episodes (6% vs. 5%, p=0.895). Hemolysis occurred following 1 bridged episode compared to 3 non-bridged episodes (3% vs.

4%, p=0.794). LDH level increased by a maximum of 58 after bridged episodes versus 105 after non-bridged episodes (p=0.526). We also analyzed the data using an INR threshold of 0.5 below target and found no additional meaningful differences in outcomes (data not shown). Similar results were also obtained when outcomes were limited to exclude patients with a prior history of bleeding or thrombotic complications (data not shown).

Table 1 - Baseline Characteristics

	Bridged (n=34)	Non-Bridged (n=76)	p Value
Number of patients	28	41	
Age	60 ± 12	62 ± 11	0.292
Male	29 (85)	61 (80)	0.527
Days since LVAD implantation	530 ± 452	596 ± 384	0.428
HeartMate II	20 (59)	36 (47)	0.267
Past medical history			
Ischemic cardiomyopathy	16 (47)	42 (55)	0.311
Major bleeding	9 (26)	28 (37)	0.287
Stroke	6 (18)	13 (17)	0.945
LVAD associated hemolysis	5 (15)	12 (16)	0.884
Atrial fibrillation	12 (35)	37 (49)	0.192
Hypertension	28 (82)	61 (80)	0.797
Diabetes	14 (41)	34 (45)	0.728
Baseline laboratory values			
Creatinine, mg/dL	1.6 ± 1.5	1.3 ± 0.4	0.136
GFR, mL/min	66 ± 27	60 ± 20	0.218
Hemoglobin, gm/dL	11.7 ± 1.4	11.5 ± 1.9	0.481
LDH, u/L	222 ± 77	214 ± 62	0.541
Risk scores			
CHA2DS2-VASc score	3.7 ± 1.6	3.9 ± 1.5	0.456
HAS-BLED score	3.7 ± 0.9	3.9 ± 1.0	0.674
ATRIA score	4.0 ± 1.9	3.6 ± 1.9	0.368
Subtherapeutic INR episode details			
Presenting INR	1.4 ± 0.2	1.6 ± 0.2	0.0001
Minimum goal INR	2.0 ± 0.1	2.0 ± 0.1	0.798
Margin from goal INR	0.6 ± 0.2	0.4 ± 0.2	0.0001
Number of days subtherapeutic	6.1 ± 4.4	9.5 ± 6.9	0.008

Values are n (%) or mean ± SD. LVAD = left ventricular assist device, GFR = glomerular filtration rate, LDH = lactate dehydrogenase, INR = international normalized ratio.

Table 2 - Three Month Adverse Event Rates			
	Bridged (n=34)	Non-Bridged (n=76)	p Value
All-cause hospitalization	17 (50)	31 (41)	0.368
Bleeding	4 (12)	13 (17)	0.474
Ischemic cerebrovascular event	2 (6)	4 (5)	0.895
Hemolysis	1 (3)	3 (4)	0.794
Maximum change in LDH, u/L	+58 ± 96	+105 ± 426	0.526
Values are n (%) or mean ± SD. LDH = lactate dehydrogenase.			

Subgroup Analysis

Subtherapeutic INR episodes were divided by CHA2DS2-VASc score between those with scores of ≤ 3 (n=47) and those with scores > 3 (n=63). The average CHA2DS2-VASc score within the entire cohort was 3.9, 2.4 ± 0.6 within the low score group and 5.0 ± 1.1 within the high score group (p=0.0001). Within 3 months, 4% of those with CHA2DS2-VASc scores ≤ 3 had a subsequent thromboembolic event compared to 10% with scores > 3. Among those with CHA2DS2-VASc score > 3, there were no thromboembolic events in patients who received bridging anticoagulation compared to 6 thromboembolic events in those that were not bridged (p=0.133) (Table 3).

Table 3 - Three Month Outcomes by CHA2DS2-VASc Score						
	CHA2DS2-VASc ≤ 3			CHA2DS2-VASc > 3		
	Bridged (n=18)	Non-Bridged (n=29)	p Value	Bridged (n=16)	Non-Bridged (n=47)	p Value
CHA2DS2-VASc score	2.4 ± 0.7	2.4 ± 0.6	0.742	5.1 ± 1.1	4.9 ± 1.0	0.499
Presenting INR	1.4 ± 0.2	1.6 ± 0.1	0.016	1.4 ± 0.2	1.5 ± 0.2	0.0001
Days subtherapeutic	5.2 ± 4.6	8.1 ± 6.1	0.09	7.1 ± 4.0	10.4 ± 7.3	0.086
Adverse event rates						
All-cause hospitalization	10 (56)	9 (31)	0.096	7 (44)	22 (47)	0.832
Bleeding	1 (6)	2 (7)	0.855	3 (19)	11 (23)	0.699
Ischemic cerebrovascular event	2 (11)	0	0.067	0	4 (9)	0.228
Hemolysis	1 (6)	0	0.199	0	3 (6)	0.3
Any thromboembolic event	2 (11)	0	0.067	0	6 (13)	0.133
Maximum change in LDH, u/L	73 ± 120	30 ± 47	0.09	41	152	0.418
Values are n (%) or mean ± SD. LDH = lactate dehydrogenase, INR = international normalized ratio.						

An analysis was also done on those patients with a history of atrial fibrillation (n=49) and those without (n=61). Among those patients with atrial fibrillation, no thromboembolic events occurred in patients who received bridging anticoagulation

compared to 5 thromboembolic events in those who were not bridged (p=0.179) (Table 4).

Table 4 - Three Month Outcomes by Atrial Fibrillation Status

	Atrial Fibrillation			No Atrial Fibrillation		
	Bridged (n=12)	Non-Bridged (n=37)	p Value	Bridged (n=22)	Non-Bridged (n=39)	p Value
CHA2DS2-VASc score	3.9 ± 1.4	4.3 ± 1.5	0.442	3.6 ± 1.8	3.6 ± 1.5	0.955
Presenting INR	1.5 ± 0.2	1.6 ± 0.2	0.041	1.4 ± 0.2	1.5 ± 0.1	0.0001
Days subtherapeutic	5.4 ± 4.4	10.8 ± 7.4	0.022	6.4 ± 4.4	8.3 ± 6.3	0.216
Adverse event rates						
All-cause hospitalization	6 (50)	22 (59)	0.565	11 (50)	9 (23)	0.031
Bleeding	1 (8)	11 (30)	0.134	3 (14)	2 (5)	0.245
Ischemic cerebrovascular event	0	4 (11)	0.235	2 (9)	0	0.056
Hemolysis	0	2 (5)	0.411	1 (5)	1 (3)	0.676
Any thromboembolic event	0	5 (14)	0.179	2 (9)	1 (3)	0.258
Maximum change in LDH, u/L	68 ± 84	125 ± 416	0.641	53 ± 103	87 ± 440	0.724

Values are n (%) or mean ± SD. LDH = lactate dehydrogenase, INR = international normalized ratio.

An additional analysis was done comparing patients with relatively high presenting INRs of ≥ 1.5 (n=70) and those with lower INRs of < 1.5 (n=40). All of the thromboembolic events noted during the course of this study occurred in patients who had a presenting INR ≥ 1.5, with no thromboembolic events occurring in those with INR < 1.5 (p=0.029) (Table 5). Among those with INR > 1.5, there was no significant difference in the rate of thromboembolic events between those that were bridged and those that were not (14% vs. 11%).

Table 5 - Three Month Outcomes by Presenting INR

	INR < 1.5 (n=40)	INR ≥ 1.5 (n=70)	p Value
Received bridging	19 (49)	15 (21)	0.003
Presenting INR	1.3 ± 0.1	1.6 ± 0.1	0.0001
Minimum goal INR	2.0 ± 0.1	2.0 ± 0.1	0.136
Days Subtherapeutic	9.1 ± 7.6	8.1 ± 5.7	0.418
Adverse event rates			
All-cause hospitalization	18 (46)	30 (42)	0.693
Bleeding	8 (21)	9 (13)	0.277
Ischemic cerebrovascular event	0	6 (9)	0.062
Hemolysis	0	4 (6)	0.131
Any thromboembolic event	0	8 (11)	0.029
Maximum change in LDH, u/L	24 ± 63	127 ± 440	0.151

Values are n (%) or mean ± SD. INR = international normalized ratio,

As an assessment of bleeding risk, a comparison between patients with low versus high HAS-BLED scores and low versus high ATRIA scores was performed. Of the patients with HAS-BLED scores < 4, 4 of 45 (9%) had a subsequent bleeding event compared to 13 of 62 (20%) of those with HAS-BLED score ≥ 4 (p=0.096) (Table 6). Of the 33 patients with ATRIA scores < 4, only 1 (3%) had a subsequent bleeding event versus 16 of 77 (21%) of those with ATRIA scores ≥ 4 (p=0.018). The use of bridging anticoagulation had no significant effect on the rate of bleeding events in any of these groups (Data not shown).

Table 6 - Outcomes by Bleeding Risk Score

	Score < 4	Score ≥ 4	p Value
HAS-BLED Scores			
Number of patient episodes	45	62	
Average score	2.8 ± 0.4	4.4 ± 0.7	0.0001
All-cause hospitalization	20 (44)	28 (44)	0.977
Bleeding	4 (9)	13 (20)	0.096
Ischemic cerebrovascular event	1 (2)	5 (8)	0.199
Hemolysis	1 (2)	3 (5)	0.487
ATRIA Scores			
Number of patient episodes	33	77	
Average score	1.3 ± 1.0	4.8 ± 1.0	0.0001
All-cause hospitalization	12 (36)	36 (47)	0.314
Bleeding	1 (3)	16 (21)	0.018
Ischemic cerebrovascular event	2 (6)	4 (5)	0.855
Hemolysis	1 (3)	3 (4)	0.824

Values are n (%) or mean ± SD.

Discussion

LVADs have found widespread use as a durable form of heart replacement therapy. However, the current generation of continuous flow devices continues to be associated with high rates of rehospitalization and adverse events, particularly bleeding and thromboembolism. Beginning in 2011 a significant increase in the incidence of pump thrombosis was noted, thought to be due in part to the use of more relaxed anticoagulation standards after device implant in an effort to reduce bleeding complications.[8,9] The recent PREVENT trial showed a reduction in pump thrombosis with the adoption of stricter guidelines for post-implant management including the use of a heparin bridge until a therapeutic INR is obtained.[2] However, the efficacy and safety of bridging anticoagulation in the outpatient setting for the

routine management of subtherapeutic INR remains unclear. Maintaining therapeutic INR levels is challenging in the LVAD population with patients typically spending only 30-50% of time within therapeutic range and 18-32% of the time spent below target.[10-12] Several studies have shown that subtherapeutic anticoagulation may be a risk factor for thromboembolic complications.[13-15] An analysis of current practice patterns shows that the routine use of parenteral bridging during periods of subtherapeutic INR is common although there is significant variability regarding when to initiate bridging.[16] Our study found that within the overall cohort there was no significant difference in the rates of bleeding or thrombotic events between those subtherapeutic episodes managed with bridging anticoagulation and those that were not. However, we identified a subset of patients with a high CHA2DS2-VASc score or atrial fibrillation who had a trend toward benefit from bridging. These results suggest that individualized risk assessment may be of value when deciding bridging strategies in patients with LVADs.

Several publications have cast doubt on the need for bridging anticoagulation in non-LVAD cohorts in the setting of atrial fibrillation and mechanical heart valves. The absence of bridging anticoagulation for atrial fibrillation when cessation of warfarin was necessary was shown to be non-inferior to enoxaparin bridging and decreased the risk of major bleeding in the BRIDGE trial.[17] The ORBIT-AF trial also showed higher rates of bleeding and adverse events associated with the use of peri-procedural bridging for atrial fibrillation.[18] A recent study including over 12,000 episodes of anticoagulation interruption among all patients on warfarin therapy found no overall benefit and higher risk of thrombotic events and other complications with enoxaparin bridging, and these results held true in the subset of patients with mechanical heart valves.[19] These authors speculated that the counterintuitive increased rate of thrombotic events associated with enoxaparin was likely due to underlying factors such that patients at higher baseline risk were more likely to be given bridging anticoagulation. The recent 2017 update in the AHA/ACC guidelines for management of valvular heart disease reflected these results by downgrading their recommendation for peri-procedural bridging anticoagulation for mechanical heart valves from class I to class IIa.[20]

Within the LVAD population, one small study of 18 patients who received 27 courses of half-dose enoxaparin (0.5 mg/kg every 12 hours) for subtherapeutic INR showed no major bleeding or thrombotic events during the treatment period, however 3 patients had a subsequent thrombotic event between 1 and 3 months after bridging.[21] More recently a paper by Bhatia, et al. including 118 LVAD patients compared adverse outcomes in those who received bridging anticoagulation with enoxaparin at any time during the study period versus those who did not receive enoxaparin.[7] The authors found that enoxaparin was associated with an increased risk of bleeding events as well as a trend towards a higher incidence of thromboembolic events in the enoxaparin group. While our results similarly show a lack of efficacy in preventing thrombotic events, there are several key differences between our study and that by Bhatia. That study utilized a

patient-based cohort approach and evaluated outcomes in patients who received enoxaparin at any time during the study period, including post-implant and periprocedural bridging. In our study we used an episode-based cohort approach comparing outcomes following individual episodes of subtherapeutic INR for a specific time period of three months in order to capture adverse events that were more likely to be related to the episode of subtherapeutic anticoagulation. In addition, while the question of post-implant and periprocedural bridging is an important one, we included only stable outpatients who were noted to have subtherapeutic INR on routine testing in order to address this specific clinical scenario. It is also worth noting that Bhatia reported an average bridging duration of 18.8 days compared to 6.1 days in our study, which may account for the trend toward increased bleeding rates associated with bridging reported in that study. Regarding the efficacy of bridging anticoagulation in preventing thromboembolic events, our results showed no overall significant difference in the rates of ischemic stroke or hemolysis between bridged and non-bridged groups. Higher CHA2DS2-VASc risk scores have previously been associated with a higher risk of thromboembolic events in LVAD patients.[22] We hypothesized that CHA2DS2-VASc scores may identify patients at higher risk of thromboembolic events who may therefore derive more benefit from bridging anticoagulation. Our results suggest that bridging anticoagulation may be helpful in preventing thromboembolic events in patients with scores > 3. Additionally, our analysis suggests that the presence of atrial fibrillation may be another factor associated with benefit from the use of bridging anticoagulation. However, these findings were not statistically significant due to a low power within these subgroups. The presenting INR of the subtherapeutic episode did not prove to be beneficial in guiding anticoagulation management.

Regarding the safety of bridging anticoagulation, we found no significant difference in the rate bleeding events between the bridged and non-bridged groups. Previous studies have shown that higher HAS-BLED bleeding risk scores correlate with higher bleeding rates in LVAD patients,[22,23] and our results show a similar trend. However, we found that bleeding event rates were similar regardless of bridging anticoagulation and therefore this score was not helpful in guiding management. The ATRIA bleeding risk score, which to our knowledge has not previously been utilized in the LVAD population, similarly showed higher scores were associated with higher bleeding rates, but the score was not beneficial in this cohort to risk stratify patients in a way that would alter decision making for bridging.
This study has multiple limitations. It was a retrospective single-center study with all baseline and adverse event data gathered via review of the medical records. Decision regarding bridging was at the discretion of the treating heart failure cardiologist although there were no significant differences in demographics or bleeding and thrombotic risk scores between the groups. Our analysis was based on INR measurements reported by the Alere home INR monitoring service and not all measurements were verified by repeat laboratory testing. The frequency and interval of repeat INR testing after the initial subtherapeutic episode was not protocolized and therefore may have been inconsistent. Patient compliance with

enoxaparin was not assessed. All adverse events occurring within 3 months of a subtherapeutic INR episode were associated with that episode although patients may have had additional fluctuations in INR, high or low, during that 3-month period. Our patient population was restricted to stable outpatients noted to have subtherapeutic INR on routine testing and our results may not be applicable to bridging in the immediate post-implant setting or peri-procedural bridging. Compared to the INR cutoff used in this study, there may exist a lower INR threshold that would show a benefit with bridging. However, our number of patients with very low INRs was too small for meaningful analysis.

In conclusion, there was no benefit associated with the routine use of bridging anticoagulation in a general population of stable LVAD outpatients with subtherapeutic INR. However, bridging anticoagulation may be beneficial in a subset of patients who are at higher risk for thromboembolic events as identified by a CHA2DS2-VASc score of > 3 or the presence of atrial fibrillation. Bridging anticoagulation should be used with caution and requires an individualized assessment of a patient's bleeding and thromboembolic risk with larger prospective studies needed to verify these findings.

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