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Standard Versus Higher Intensity Anticoagulation for Patients With Mechanical Aortic Valve Replacement and Additional Risk Factors for Thromboembolism

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Standard Versus Higher Intensity Anticoagulation for Patients With Mechanical Aortic Valve Replacement and Additional Risk Factors for Thromboembolism

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Current guidelines recommend targeting an international normalized ratio (INR) of 2.5 to 3.5 for patients with mechanical aortic valve replacement (AVR) and additional risk factors for thromboembolic events. Available literature supporting the higher intensity (INR) goal is lacking. We aimed to evaluate the association of standard and higher intensity anticoagulation on outcomes in this patient population. The Michigan Anticoagulation Quality Improvement Initiative database was used to identify patients with mechanical AVR and at least one additional risk factor. Patients were classified into 2 groups based on INR goal: standard-intensity (INR goal 2.5) or higher-intensity (INR goal 3.0). Cox-proportional hazard model was used to calculate adjusted hazard ratios. One hundred and forty-six patients were identified of whom 110 (75.3%) received standard-intensity anticoagulation and 36 (24.7%) received higher intensity anticoagulation. Standard-intensity patients were older and more likely to be on aspirin. Atrial fibrillation was the most common additional risk factor for inclusion. The primary outcome of thromboembolic events, bleeding, or all-cause death was 13.9 and 19.5/100-person-years in the standard-intensity and higher intensity groups, respectively (adjusted HR 2.58, 95% confidence interval 1.28 to 5.18). Higher-intensity anticoagulation was significantly associated with any bleeding (adjusted HR 2.52, 95% confidence interval 1.27 to 5.00) and there were few thromboembolic events across both groups (5 events total). These results challenge current guideline recommendations for anticoagulation management of mechanical AVR in patients with additional risk factors. **(Am J Cardiol 2021;159:100−106)**

The American College of Cardiology (ACC) recommends an international normalized ratio (INR) goal of 3.0 (2.5 to 3.5) for patients with a mechanical aortic valve replacement (AVR) and additional risk factors for thromboembolic events, including atrial fibrillation (AF), previous thromboembolism, left ventricular (LV) dysfunction, or hypercoagulable conditions.[1] The European Society of Cardiology has similar recommendations.[2] This higher anticoagulation intensity is given a strong recommendation despite a lack of published evidence to support it. The 9th edition American College of Chest Physicians clinical practice guideline for valvular disease removed their recommendation for the higher INR target in this population due to lack of evidence demonstrating additional benefit over harm.[3] The current body of literature comparing INR targets in patients with mechanical valves does not adequately address strategies in these "higher risk" populations[4−8] leading to practice variability in anticoagulation intensity for these patients. In this study, we assessed the efficacy and safety of anticoagulation management in this patient population, comparing patients on standard-intensity anticoagulation (INR goal 2.5, target range 2.0 to 3.0) versus guideline-recommended higher intensity anticoagulation (INR goal 3.0, target range 2.5 to 3.5).

Methods

This was a multicenter, retrospective registry analysis utilizing deidentified data from patients enrolled in the Michigan Anticoagulation Quality Improvement Initiative (MAQI^2) database between November 2009 and September 2020. MAQI^2 is a collaborative of 6 outpatient anticoagulation clinics across the state of Michigan sponsored by Blue Cross-Blue Shield of Michigan.

Eligible patients included those ≥18 years of age with a mechanical AVR receiving standard-intensity or higher intensity warfarin. The target INR goal range is selected by patient's physician at the time of enrollment into the anticoagulation clinics. Warfarin dose adjustments are managed

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by the anticoagulation clinic and few patients undergo home INR testing. Standard intensity warfarin was defined as patients with an INR goal range of 2.0 to 3.0. Guideline-recommended higher-intensity warfarin was defined as patients with an INR goal range of 2.5 to 3.5. All patients were required to have at least 1 of the following risk factors: AF, previous thromboembolism, LV systolic dysfunction or hypercoagulable condition. Previous thromboembolism was defined as previous transient ischemic attack, cerebrovascular accident, or history of systemic arterial embolism. LV systolic dysfunction was defined as ejection fraction <45%. Patients were excluded if they had a bioprosthetic AVR, known nonbileaflet or older generation mechanical AVR (i.e., ball-in-cage), or mechanical mitral valve replacement. Patients were also excluded if they had an INR goal range that did not meet study inclusion criteria.

The primary end point was a composite of thromboembolic events, any bleed, and all-cause death. Bleeding outcomes were defined based on the International Society of Thrombosis and Hemostasis (ISTH) criteria.[9,10] Minor bleeding is any bleeding that does not meet criteria for major or clinically relevant non-major (CRNM) bleeding. Secondary end points included components of the primary composite end point, any bleed, emergency department visits, any hospitalization, hospitalization for bleeding, red-blood cell (RBC) transfusion, and vitamin K administration.

Categorical variables were assessed using Chi square test and continuous variables were assessed using *t* tests for comparing baseline characteristics. For the primary and secondary end points, differences in event rates were compared by Poisson test and reported as 95% confidence interval (CI) and p-values. Two-sided p-values <0.05 were considered significant for all comparisons. Cox-proportional hazard models were fitted to assess the relations between outcomes and standard versus higher intensity INR target and key demographic or clinical characteristics. AF, former tobacco use, Charlson Comorbidity index and HAS-BLED score were identified as key clinical characteristics. Age, aspirin use, and time in therapeutic range <60% are components of the HAS-BLED score and therefore were not assessed in the models individually. All statistical analyses were carried out using SAS version 9.4 (SAS Institute Cary, North Carolina) and R-64 version 3.6.1. Institutional regulatory board approval was obtained at all participating centers.

Results

Among the 14,625 warfarin-treated patients enrolled in the MAQI^2 database, 265 (1.8%) patients had a mechanical aortic valve replacement with an INR goal of 2.0 to 3.0 or 2.5 to 3.5. Of these patients, 146 (55.1%) had at least 1 of the specified risk factors for thromboembolism and met inclusion criteria (Figure 1). Of the 146 included patients, 110 (75.3%) patients were in the standard-intensity group and 36 (24.7%) patients were in the higher-intensity group. Patients in the standard-intensity group were older, more likely to have AF, and had a higher Charlson Comorbidity index (Table 1). Aspirin use was also more frequent in the standard-intensity group. The mean HAS-BLED score was 3.2 ± 1.3 and 2.9 ± 1.5 and follow-up time was 2.0 ±2.1 and 2.6 ± 2.9 years in the standard and higher intensity groups, respectively.

The primary composite outcome of all cause death, any bleeding or thrombotic complication occurred at a rate of 13.9 events per 100-patient-years in the standard-intensity group (95% CI 11.7 to 16.4) and 19.5 events per 100-patient-years in the higher-intensity group (95% CI 16.9 to 22.4), p = 0.003 (Table 2). Thromboembolic event rates were low and occurred in 3 patients in the standard-intensity group and 2 patients in the higher intensity group. There were fewer major bleeding events in the standard-intensity group, 3.1 events versus 5.4 events per 100-patient-years, p = 0.02. Hospitalization for bleeding and nonbleeding as well as RBC transfusion, occurred more frequently in the higher intensity group. All-cause death was similar between groups (Table 2).

After adjusting for key baseline characteristics, anticoagulation intensity was a significant predictor of the primary outcome (adjusted hazard ratio [aHR] 2.58, CI 1.28 to 5.18; Figure 2), and any bleeding event (aHR 2.52, CI 1.27 to 5.00; Figure 3). HAS-BLED score was also a significant predictor of the primary outcome (aHR 1.97, CI 1.30 to 2.98), any bleeding event (aHR 2.31, CI 1.55 to 3.44) and major/CRNM bleeding (aHR 1.89, CI 1.08 to 3.30; Figures 2−4).

Discussion

In this multicenter, observational cohort study of patients with mechanical AVR and additional risk factors, standard-intensity anticoagulation was associated with a lower composite end point of death, any bleeding, and thromboembolic complication compared with the higher intensity anticoagulation recommended by ACC guidelines. Standard-intensity anticoagulation was associated with fewer major bleeding events as well as hospitalization due to bleeding. This reduction occurred despite higher rates of concurrent low-dose aspirin use in patients with standard-intensity warfarin. In adjusted analysis, higher intensity anticoagulation remained significantly associated with the composite outcome and any bleeding event.

Available data supports an INR of goal 2.0-3.0 for bileaflet or current-generation single-tilting disc mechanical AVR with normal sinus rhythm without an enlarged left atrium.[8] This is consistent with the ACC and European Society of Cardiology valvular guideline recommendations.[1,2] Historic use of higher INR targets and observational studies associating key predictors with thromboembolism risk[11−15] have been used to justify a higher INR target in patients with additional thromboembolic risk factors.[1,2,16] However, most data comparing anticoagulation strategies in mechanical valve patients, with or without additional thromboembolic risk factors, do not demonstrate benefit with higher intensity anticoagulation.[17−19]

To our knowledge, this is the only study to date evaluating anticoagulation intensity for mechanical AVR exclusively in patients with additional thromboembolic risk factors. In 2007, the ESCAT II trial compared a "conventional" INR range of 2.5 to 4.5 to a "low" range

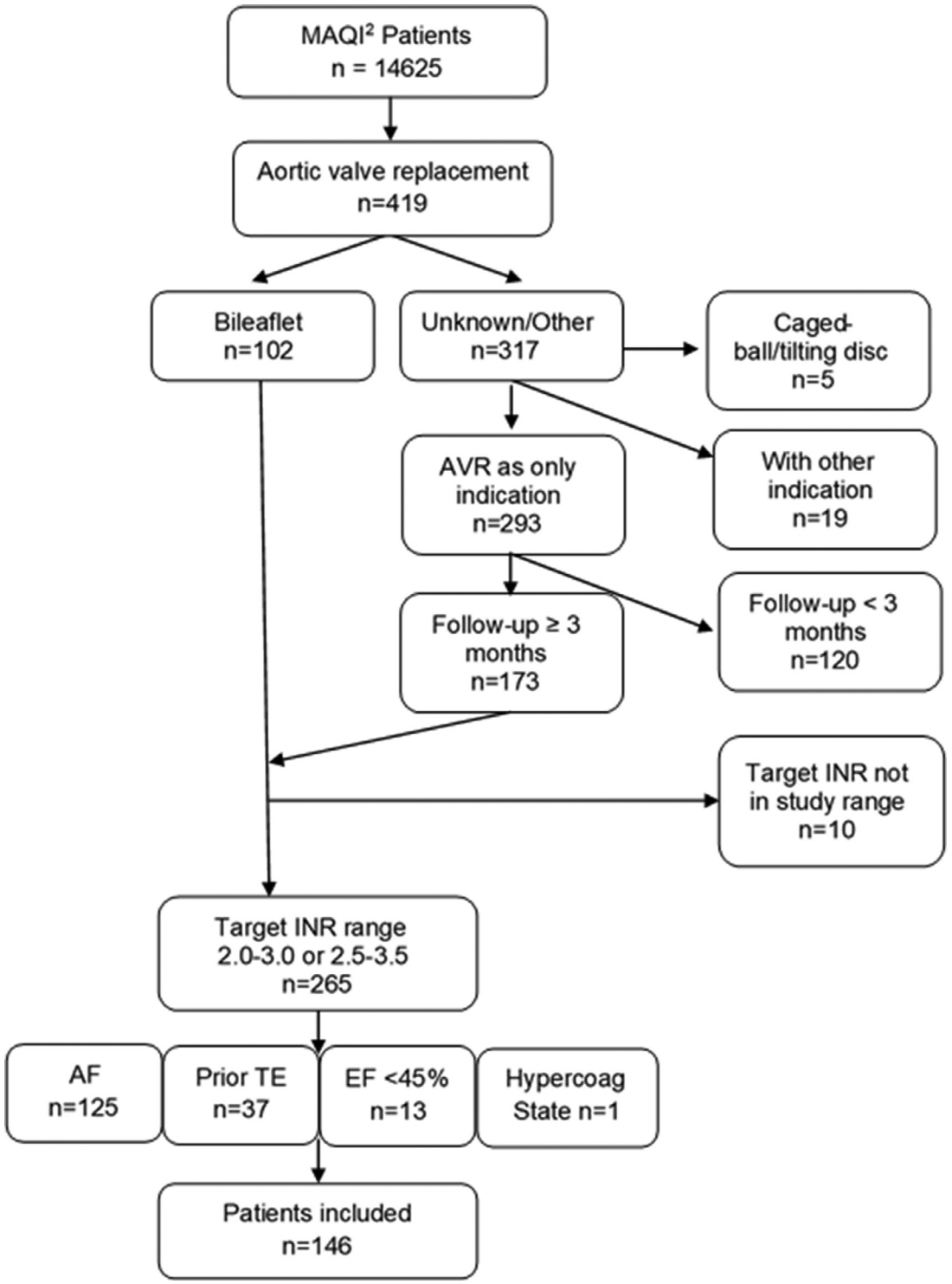

Figure 1. Screening criteria and patient selection. Patients may meet more than one thromboembolic risk criteria. AVR = aortic valve replacement; AF = atrial fibrillation; EF = ejection fraction; Hypercoag = hypercoagulable; INR = international normalized ratio; TE = thromboembolism.

of 1.8 to 2.8 for AVR or 2.5 to 3.5 for mitral valve replacement or double valve replacement in a randomized trial of 2,673 patients.[17] Roughly 25% of patients had left ventricular ejection fraction <30% and 15% of patients had AF. Patients with AVR in the conventional group experienced thromboembolic complications at a rate of 0.46 versus 0.24 per patient-year in the low group and a rate of bleeding complication at 1.78 versus 1.42 per patient-year, respectively. No statistical differences were found in the event rates and the authors concluded that a lower INR range does not increase thromboembolic risk. They also noted that in both INR ranges, bleeding events

Table 1
Patient characteristics of standard-intensity versus high-intensity

	Standard intensity N = 110	High intensity N = 36	p-value
Age (years), mean ± SD	69.3 ± 13.9	56.7 ± 16.9	<0.001
Men	66 (60%)	21 (58%)	0.86
Weight (kg), mean ± SD	87.9 ± 22.2	82.4 ± 18.0	0.19
BMI (kg/m^2), mean ± SD	30.0 ± 6.6	28.0 ± 5.2	0.10
Smoker	10 (9%)	6 (17%)	0.21
Atrial fibrillation	99 (90%)	26 (72%)	0.01
LV dysfunction, EF ≤45%	7 (6%)	5 (14%)	0.15
Previous thromboembolism	24 (22%)	13 (36%)	0.09
Hypercoagulable state	1 (1%)	0	-
CAD	69 (63%)	18 (50%)	0.18
PCI/CABG	37 (34%)	8 (22%)	0.2
Heart failure	45 (41%)	14 (39%)	0.83
Diabetes mellitus	30 (27%)	8 (22%)	0.55
HTN	77 (70%)	27 (75%)	0.57
Arrhythmia	74 (67%)	22 (61%)	0.50
Liver disease	4 (4%)	2 (6%)	0.64
Chronic kidney disease	15 (14%)	6 (17%)	0.65
Prior cerebrovascular accident or transient ischemic attack	23 (21%)	13 (36%)	0.07
Prior DVT/PE	7 (6%)	1 (3%)	0.68
Bleeding (≤30 days)	12 (11%)	1 (3%)	0.19
Bleeding (>30 days)	5 (5%)	3 (8%)	0.41
Prior gastrointestinal bleed	11 (10%)	4 (11%)	1.00
Heavy alcohol or drug use	5 (4%)	4 (11%)	0.22
Former tobacco use	40 (36%)	6 (17%)	0.03
Falls	5 (4%)	1 (3%)	1.00
Peripheral arterial disease	12 (11%)	2 (8%)	1.00
HAS-BLED score, mean ± SD	3.2 ± 1.3	2.9 ± 1.5	0.18
Charlson-Comorbidity Index, mean ± SD	5.1 ± 2.1	3.9 ± 2.5	0.007
Medications			
Aspirin >100 mg	3 (3%)	0	-
Aspirin ≤ 100 mg	82 (75%)	20 (56%)	0.03
NSAIDs	1 (1%)	0	-
Clopidogrel, ticlopidine, prasugrel, ticagrelor, antiplatelets-other	2 (2%)	2 (6%)	0.25
Beta Blocker	84 (76%)	25 (69%)	0.41
ACEI and/or ARB	45 (41%)	15 (42%)	0.94
>1 antiplatelet agent	1 (1%)	2 (6%)	0.15
Proton pump inhibitor	31 (28%)	10 (28%)	0.96
TTR, mean ± SD	0.60 ± 0.17	0.54 ± 0.16	0.06
Warfarin dose changes per year, median (IQR)	10.8 (6.2−20.9)	11.8 (7.1−22.9)	0.7
Follow-up (years), mean ± SD	2.0 ± 2.1	2.6 ± 2.9	0.22

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; CABG = coronary bypass grafting; DVT = deep vein thrombosis; HTN = hypertension; IQR = interquartile range; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PE = pulmonary embolism; SD = standard deviation; TTR = time in the therapeutic range.

exceed thromboembolism event rates. Target INR range, left ventricular ejection fraction category and AF were not associated with events in logistic regression analysis. The LIWACAP trial similarly found no difference in thromboembolic risk between patients who received "standard intensity" anticoagulation (INR goal 3.0 to 4.5) or "low-intensity" (INR goal 2.0 to 3.0) anticoagulation plus 100 mg aspirin in 198 patients undergoing AVR or mitral valve replacement.[18] Within this population, roughly 30% of patients had additional thromboembolic risk factors.

Most recently in 2014, the PROACT trial compared an INR goal of 2.0−3.0 to 1.5−2.0 after 3 postoperative months in On-X AVR patients.[19] All 375 patients in both groups received low-dose aspirin. Unlike previous studies, PROACT specifically enrolled patients with at least 1 thromboembolic risk factor. However, unique to this study, a lack of platelet response to aspirin or clopidogrel was also considered a risk factor for thromboembolism, accounting for roughly 65% of patients enrolled. At the end of the 4-year follow-up, thromboembolism and valve thrombosis occurred at a rate of 2.96 and 1.85 per patient-year in the

Table 2
Efficacy and safety outcomes

	Standard intensity (n = 110)		Higher intensity (n = 36)		p-value (event rate)
	Total events	Event Rate per 100py (95% CI)	Total events	Event Rate per 100py (95% CI)	
Total adverse events (Thrombotic, Bleeding, or all-cause death)	31 (28%)	13.9 (11.7, 16.4)	18 (50%)	19.5 (16.9, 22.4)	0.003
Thromboembolic events (Any)	3 (3%)	1.4 (0.8, 2.3)	2 (6%)	2.2 (1.4, 3.3)	0.23
Ischemic/Embolic stroke	3 (3%)	1.4 (0.8, 2.3)	1 (3%)	1.1 (0.5, 2.0)	0.69
Other	0	0	1 (3%)	1.1 (0.5, 2.0)	-
First bleed (Any)	27 (25%)	12.1 (10, 14.5)	15 (42%)	16.2 (13.8, 18.9)	0.02
ISTH Major	7 (6%)	3.1 (2.1, 4.4)	5 (14%)	5.4 (4.1, 7.0)	0.02
ISTH CRNM	16 (15%)	7.2 (5.6, 9.1)	6 (17%)	6.5 (5, 8.3)	0.61
Minor bleed	22 (20%)	9.9 (8.0, 12.1)	13 (36%)	14.2 (11.9, 16.6)	0.008
ED visit	44 (40%)	19.7 (17.0, 22.7)	20 (56%)	21.7 (18.9, 24.8)	0.35
Hospitalization (Any)	32 (29%)	14.4 (12.1, 17.0)	17 (47%)	18.4 (15.8, 21.3)	0.03
For bleeding	9 (8%)	4.0 (2.9, 5.4)	6 (17%)	6.5 (5.0, 8.3)	0.02
Indication other than bleeding	26 (24%)	11.7 (9.7, 14.0)	16 (44%)	17.3 (14.8, 20.1)	0.001
RBC transfusion	3 (3%)	1.4 (0.8, 2.3)	6 (17%)	6.5 (5.0, 8.3)	<0.001
Given Vitamin K	8 (7%)	3.6 (2.5, 5.0)	3 (8%)	3.3 (2.3, 4.6)	0.81
Given FFP	2 2%)	0.9 (0.4, 1.7)	1 (3%)	1.1 (0.5, 2.0)	0.82
Death	5 (5%)	2.2 (1.4, 3.3)	2 (6%)	2.2 (1.4, 3.3)	1.00

CRNM = clinically relevant non-major; ED = emergency department; FFP = fresh frozen plasma; ISTH = International Society of Thrombosis and Hemostasis; RBC = red blood cell.

low and control INR groups, respectively (HR 1.6 [0.81 to 3.17], p = 0.178). Major bleeding was significantly lower in the low INR group, 1.48 versus 3.31 per patient-year, respectively (HR 0.45 [0.21 to 0.94], p=0.032). Although this trial demonstrates the ability to lower the INR goal in aortic On-X valves 3 months postoperatively, due to the broad inclusion criteria for thromboembolic risk factors, conclusions could not be drawn regarding appropriate anticoagulation strategies in high risk patients. Thus, the ACC valvular guidelines only recommend considering this strategy in patients without thromboembolic risk factors.[1]

Our study has several limitations. Although data from 6 anticoagulation clinics were pooled, the sample size remained relatively small. This limited the ability to

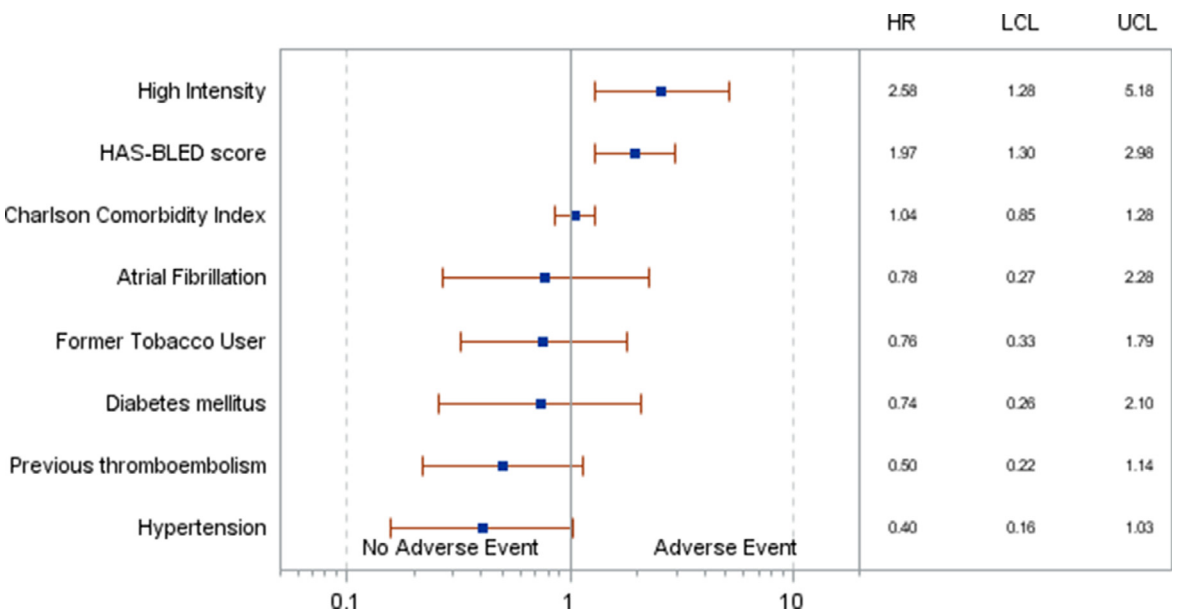

Figure 2. Cox-proportional hazard model assessing variables associated with the primary outcome. AF=atrial fibrillation; CCI = Charlson Comorbidity index.

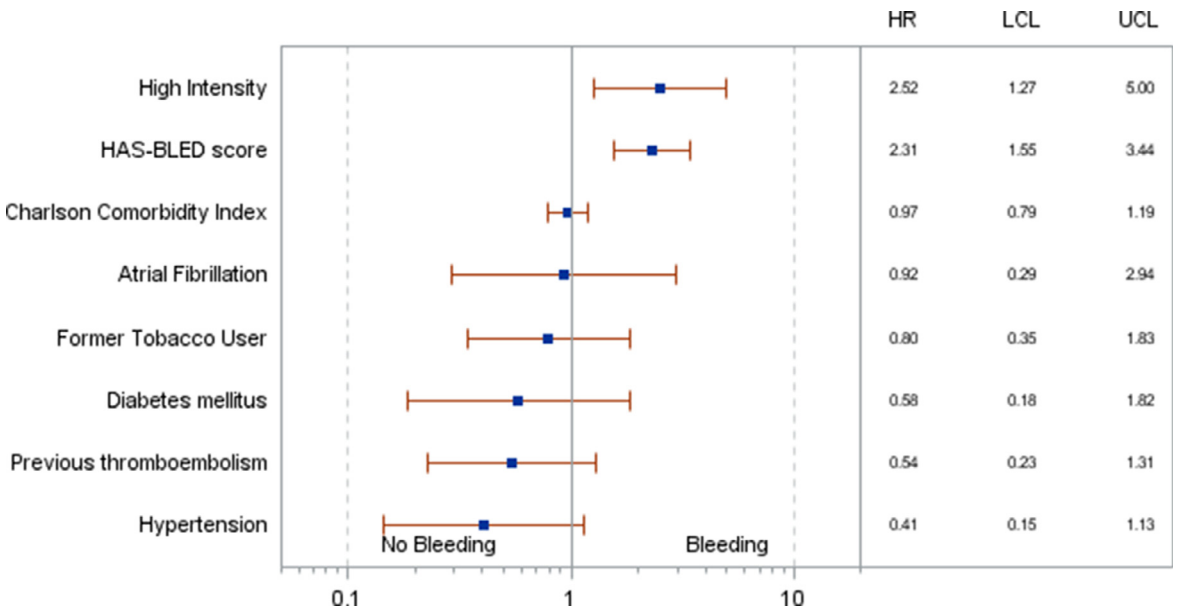

Figure 3. Cox-proportional hazard model assessing variables associated with any bleeding. AF = atrial fibrillation; CCI = Charlson Comorbidity index.

demonstrate significant differences between groups and impact of baseline characteristics on thromboembolism, which occurred infrequently. Interestingly, of patients with mechanical AVR, 53% had a thromboembolic risk factor, demonstrating this is a frequently encountered clinical situation for these patients. The retrospective design increases the risk for unaccounted baseline differences and unmeasured confounding between groups that may have impacted outcomes. Notably, nonbleeding hospitalizations were higher in the higher-intensity group, which may reflect residual confounding related to baseline characteristic differences. Aspirin use was higher in the standard-intensity group and could have impacted thromboembolic outcomes even after inclusion in the multivariable analysis. Risk factors for thromboembolism were assessed at baseline only and any changes across the follow-up period were not captured. Finally, the results cannot demonstrate causation and may not be generalizable to patients managed in other geographic regions.

In conclusion, standard-intensity anticoagulation (INR goal 2.0 to 3.0) is associated with lower bleeding rates than higher-intensity anticoagulation commonly recommended by society guidelines (INR goal 2.5 to 3.5) for patients with mechanical AVR and thromboembolic risk factors. Reassuringly, few patients in either treatment group experienced thromboembolic complications. These data support the need

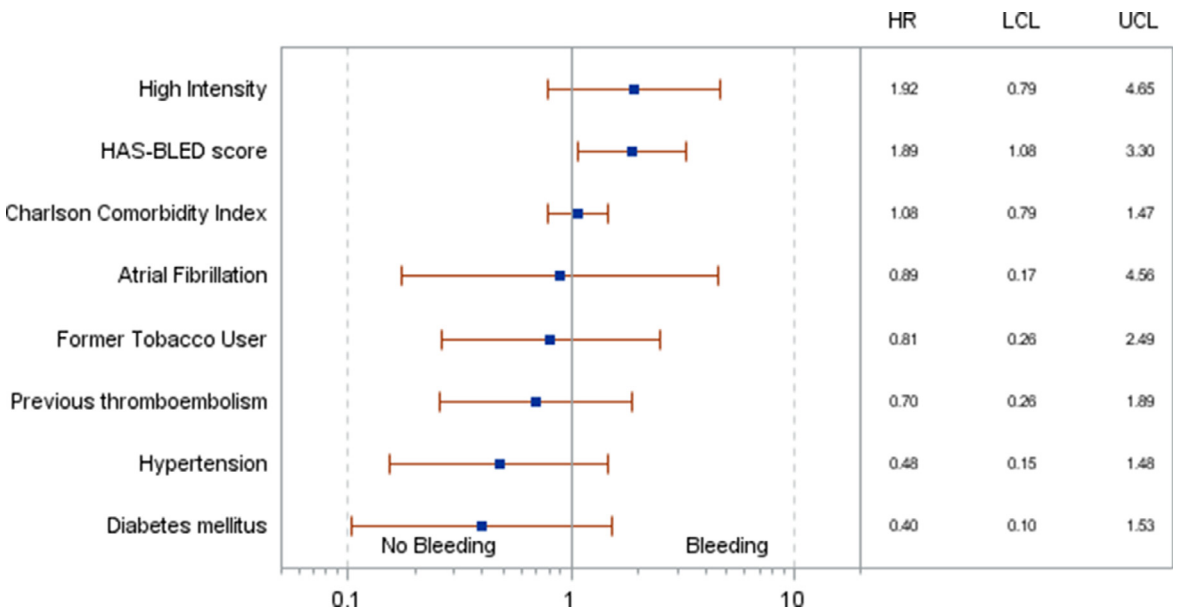

Figure 4. Cox-proportional hazard model assessing variables associated with major or CRNM bleeding. AF = atrial fibrillation; CCI = Charlson Comorbidity index.

for randomized trials to assess the risks and benefits associated with standard- versus higher intensity anticoagulation in patients with AVR and thromboembolic risk factors.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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