

Bleeding Risk and Antithrombotic Strategy in Patients With Sinus Rhythm and Heart Failure With Reduced Ejection Fraction Treated With Warfarin or Aspirin

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We sought to assess the performance of existing bleeding risk scores, such as the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score or the Outpatient Bleeding Risk Index (OBRI), in patients with heart failure with reduced ejection fraction (HFrEF) in sinus rhythm (SR) treated with warfarin or aspirin. We calculated HAS-BLED and OBRI risk scores for 2,305 patients with HFrEF in SR enrolled in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial. Proportional hazards models were used to test whether each score predicted major bleeding, and comparison of different risk scores was performed using Harell *C*-statistic and net reclassification improvement index. For the warfarin arm, both scores predicted bleeding risk, with OBRI having significantly greater *C*-statistic (0.72 vs 0.61; $p = 0.03$) compared to HAS-BLED, although the net reclassification improvement for comparing OBRI to HAS-BLED was not significant (0.32, 95% confidence interval [CI] -0.18 to 0.37). Performance of the OBRI and HAS-BLED risk scores was similar for the aspirin arm. For participants with OBRI scores of 0 to 1, warfarin compared with aspirin reduced ischemic stroke (hazard ratio [HR] 0.51, 95% CI 0.26 to 0.98, $p = 0.042$) without significantly increasing major bleeding (HR 1.24, 95% CI 0.66 to 2.30, $p = 0.51$). For those with OBRI score of ≥ 2 , there was a trend for reduced ischemic stroke with warfarin compared to aspirin (HR 0.56, 95% CI 0.27 to 1.15, $p = 0.12$), but major bleeding was increased (HR 4.04, 95% CI 1.99 to 8.22, $p < 0.001$). In conclusion, existing bleeding risk scores can identify bleeding risk in patients with HFrEF in SR and could be tested for potentially identifying patients with a favorable risk/benefit profile for antithrombotic therapy with warfarin. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;■:■–■)

Patients with heart failure with reduced ejection fraction (HFrEF) may be at increased risk for ischemic strokes because of left ventricular thrombus formation and

subsequent embolism.^{1,2} Randomized clinical trials, such as the Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial³ and the Warfarin versus Aspirin in Reduced

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See page 8 for disclosure information.

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¹The full list of WARCEF investigators is provided in the Supplementary File.

Table 1

Calculation of the HAS-BLED and OBRI risk scores. All risk factors are scored as 1 point each unless otherwise noted. Because the HAS-BLED risk score was derived in patients on anticoagulation therapy, and because no patient in warfarin received both aspirin and warfarin concurrently, aspirin use in the HAS-BLED score was coded as 0 in this analysis. Similarly, for patients assigned to aspirin, the item for labile INR in the HAS-BLED score was coded as 0 for these patients. For abnormal liver function, based on available data in WARCEF, a cut-off for AST level of >114 IU/L was used

HAS-BLED Risk Score	OBRI Risk Score
Hypertension (SBP >160 mm Hg)	Age >65 years
Abnormal renal/ liver function (1 point for each)	History of stroke
Stroke	History of GIB
Bleeding	Recent MI, HCT <30%, Cr >1.5 mg/dL, or diabetes mellitus
Labile INRs (TTR <60%)	
Elderly (age >65 years)	
Drugs (antiplatelet agents / NSAIDs) or excess alcohol (1 point for each)	

Cr = creatinine; GIB = gastrointestinal tract bleeding; HCT = hematocrit; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drugs; SBP = systolic blood pressure; TTR = time in therapeutic range.

Table 2

Characteristics of WARCEF participants by warfarin versus aspirin and by major bleeding status during follow-up

Variable	Warfarin			Aspirin		
	Major bleeding (n=66)	No major bleeding (n=1076)	p-value	Major bleeding (n=31)	No major bleeding (n=1132)	p-value
Age >65 yrs old	36 (55%)	358 (33%)	< 0.001	13 (42%)	389 (34%)	0.420
Women	21 (32%)	215 (20%)	0.021	8 (26%)	216 (19%)	0.349
Non-Hispanic white	45 (68%)	814 (76%)	0.182	24 (77%)	855 (76%)	0.866
Non-Hispanic black	9 (14%)	157 (15%)		5 (16%)	161 (14%)	
Hispanic	9 (14%)	76 (7%)		1 (3%)	80 (7%)	
Other	3 (6%)	29 (3%)		1 (3%)	36 (3%)	
Body mass index (kg/m ²)			0.228			<0.001
< 25	22 (33%)	279 (26%)		16 (52%)	263 (23%)	
25-30	26 (39%)	400 (37%)		4 (13%)	452 (40%)	
> 30	18 (27%)	397 (37%)		11 (35%)	417 (37%)	
Hypertension	37 (59%)	634 (61%)	0.732	18 (62%)	678 (62%)	0.967
Diabetes mellitus	23 (35%)	348 (32%)	0.673	7 (23%)	344 (30%)	0.350
Atrial fibrillation	2 (3%)	42 (4%)	0.721	0 (0%)	42 (4%)	0.275
Myocardial infarction	33 (50%)	516 (48%)	0.747	12 (39%)	551 (49%)	0.273
Ischemic heart disease	33 (50%)	455 (42%)	0.219	9 (29%)	494 (44%)	0.105
Prior stroke or TIA	14 (21%)	141 (13%)	0.062	8 (26%)	131 (12%)	0.016
Renal impairment	4 (6%)	22 (2%)	0.033	2 (6%)	16 (1%)	0.026
Liver impairment	2 (3%)	39 (4%)	0.321	2 (6%)	36 (3%)	0.646
Anemia, defined as hematocrit < 30%	1 (2%)	3 (0.3%)	0.106	0 (0%)	3 (0.3%)	0.777
Smoking status			0.549			0.347
Current	10 (15%)	203 (19%)		6 (19%)	189 (17%)	
Former	38 (58%)	547 (51%)		19 (61%)	585 (52%)	
Never	18 (27%)	326 (30%)		6 (19%)	358 (32%)	
Alcohol consumption			0.240			0.025
Current, > 2oz/day	17 (26%)	262 (24%)		6 (19%)	287 (25%)	
Previous, >2oz/day	9 (14%)	241 (22%)		13 (42%)	243 (21%)	
Never	40 (60%)	573 (53%)		12 (39%)	602 (53%)	
NYHA classification			0.898			0.916
I	8 (12%)	146 (14%)		5 (16%)	163 (14%)	
II	35 (53%)	596 (55%)		18 (58%)	643 (57%)	
III	22 (33%)	324 (30%)		8 (26%)	311 (27%)	
IV	1 (2%)	10 (1%)		0 (0%)	15 (1%)	
LV ejection fraction (%)	25.3±7.3	24.5±7.5	0.426	24.7±6.1	24.8±7.6	0.932
TTR <60%	33 (52%)	465 (46%)	0.349	NA	NA	NA

Renal impairment is defined as creatinine clearance of <30 ml/min; liver impairment is defined as AST level of >114 IU/L, which represents three times the upper limit of normal.

Bold values denote p-values less than 0.05.

NYHA = New York Heart Association; TIA = transient ischemic attack; TTR = time in therapeutic range.

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