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DOI:
10.1016/j.amjcard.2017.06.058

Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism

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Article type: Review article

Running head: Bleeding risk scores in AF and VTE

Funding: None

Abstract

Patients receiving oral anticoagulant (OAC) therapy for stroke prevention in atrial fibrillation (AF) and prevention of venous thromboembolism (VTE) face an increased risk of bleeding with OAC treatment. Clinicians need to weigh-up the benefits of OAC treatment against the risk of bleeding. To help formalise bleeding risk assessment, various bleeding risk scores have been developed to help predict the risk of bleeding in AF and VTE patients receiving anticoagulant therapy. This review summarises the literature involving original studies deriving bleeding risk scores and validation studies of these scores for stroke prevention in AF and treatment/prevention of VTE. To date, there are 10 bleeding risk scores, 6 for use if AF populations, three in VTE cohorts and 1 for mixed indications; they differ markedly in the number of, and risk factors for bleeding, and complexity. In conclusion, many clinical prediction tools to assess bleeding risk prior to starting OAC for either stroke prevention in AF or treatment of VTE are available and should be used in clinical practice to identify and manage modifiable risk factors.

Words: 174

Key words:

Bleeding risk score, atrial fibrillation, venous thromboembolism, anticoagulant therapy

Oral anticoagulants (OAC), including vitamin K antagonists (VKAs) and non-VKA oral anticoagulants (NOACs) are recommended to prevent thromboembolic events in patients with atrial fibrillation (AF) and for primary and secondary prevention of venous thromboembolism (VTE). However, OAC use is associated with an increased risk of major bleeding, the most serious of which is intracranial hemorrhage (ICH).[1] In clinical practice, estimating the bleeding risk of an individual patient is beneficial before starting an anticoagulant,[2] particularly to identify and manage modifiable bleeding risk factors. In addition bleeding risk assessment could help to identify those at higher bleeding risk for whom additional measures, such as more regular follow-up visits and good International Normalised Ratio (INR) management (for those on VKAs), providing information and/or practical measures to reduce the falls risk, and informing patients about high-risk activities[1] to reduce bleeding risk[3] could be implemented. Bleeding risk scoring systems have been developed for use in AF and VTE patients to estimate bleeding risk and to help aid treatment decisions. These scores have been tested and validated worldwide in many cohorts of AF[4-9] and VTE[10-12] to support physicians in assessing bleeding risks.[13] More recently, the European Society of Cardiology (ESC) Guidelines on the management of AF summarised bleeding risks (into modifiable, potentially modifiable, non-modifiable and biomarker-based) and encouraged prompt attention to correct modifiable bleeding risks.[14] This review summarises the original derivation and validation studies of these bleeding risk scores for stroke prevention in AF and treatment/prevention of VTE.

Methods

A literature search was performed in EMBASE (1974 to April 21 2016), EMBASE Classic (1947 to 1973), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to present). The search strategy included keywords and MeSH terms relating to bleeding risk score, major bleeding, bleeding, AF, VTE, warfarin, and oral anticoagulant individually and in combination. Primary published research articles on prospective or retrospective studies where bleeding risk scores were derived

and validated were included. Studies that did not provide comparative outcomes, information on follow up time, or were not published in the English language were excluded. A manual search of the reference lists was also performed for studies that were not retrieved by the database searches.

To date, 6 bleeding risk scores are available for use in AF populations,[4-9] 3 in VTE populations[10-12] and 1 in a mixed indication population.[15] Tables 1 to 4 summarises the main published prospective or retrospective studies where bleeding risk scores in patients with AF and VTE who are treated with warfarin were derived and/or validated.

Many different risk factors for bleeding are included in the various bleeding scores (**Table 1)**, with the number of risk factors included ranging from three[4,12] to 12.[8] All bleeding scores[4-12,15] included age, utilising different age ranges and cut-offs (ranging from > 50 years old to > 85 years old) to indicate greater risk of bleeding; four scores included age ≥75 years.[5,6,8,11] After age, the most common bleeding risk factors included in the scores were as follows: (i) previous/remote bleeding (reported in 8 scores),[4-9,11,15] (ii) renal disease (included in 7 scores),[5-8,10,11,15] (iii) anemia (in 6 scores),[5,6,8,9,11,15] malignancy (in 4 scores);[8,10-12] liver disease,[7,8,10] hypertension,[6-8] stroke,[7,8,15] combined antiplatelet therapy[5,7,9] and alcohol excess,[7-9] (all included in 3 scores), while two scores included diabetes mellitus,[9,15] reduced platelet count[8,10] and female sex.[9,12]

Other risk factors included biomarkers (high-sensitivity troponin, cTnT-hs and growth differentiation factor-15, GDF-15), recent bleed, myocardial infarction, labile INR, excessive falls risk, genetic factors, active gastro-duodenal ulcer, Intensive Care Unit/Coronary Care Unit (ICU/CCU) admission, central venous catheter, rheumatic disease, male sex and clinically overt pulmonary embolism**.** Seven[5,6,8-11,15] out of 10 studies reported patients with a history or diagnosis of cancer, as malignancy is associated with increased risk of bleeding;[12,16] about 2.5%-30% had a history/diagnosis of cancer (**Table 2**). All 3[10-12] bleeding scores for VTE patients include history or current diagnosis of cancer in their bleeding score, as cancer is shown to increase the risk of thromboembolism.[17,18] Interestingly the ORBIT [5]

score and the score developed by Ruiz-Gimenez et al[11] found almost 60% of their population had anemia, also a known risk factor for bleeding. In most bleeding scores[4-7,9] for AF, hypertension was the most prevalent co-morbidity followed by congestive heart failure and diabetes.

Clinically overt PE was included as a risk factor for bleeding only in the VTE bleeding score by Ruiz-Gimenez et al.[11] The aim of the other 2 VTE scores[10,12] was to develop a score with the ability to distinguish patients at low, mild or high risk of major bleeding during the first 90 days of OAC therapy. Kuijer et al[12] constructed the simplest bleeding risk prediction score, including only 3 clinical factors for patients at high risk of developing hemorrhagic complications at OAC inception, however this level of simplicity may miss other important features that could put patients at risk of bleeding.

Two bleeding risk scores, $HEMORR_2HAGES$[8] and the ABC bleeding score,[4] included factors that are not routinely available in daily clinical practice. $HEMORR_2HAGES$ included genetic testing, although this was not available in their cohort, and the ABC score included 2 biomarkers, GDF-15 and cTnT-hs.

The mean/median age of study population in the derivation cohort ranged from 61[15] to 80.2 years[8] **(Table 2)**. Almost half of the population in the derivation studies were female and only 3 studies[5,6,15] reported ethnicity, which was predominantly White. Five out of 6[4-7,9] studies from the AF cohorts reported hypertension as the most common co-morbid disease present in their population whereas one study from a VTE cohort[10] and the mixed cohort[15] reported kidney disease to be more prevalent in their patient population.

Table 3 presents the characteristics of derivation and validation studies of bleeding risk scores for AF and VTE. A prospective study design was used in 3[4,5,7] out of 6 scores for AF populations and 2[10,11] out of 3 studies in VTE populations. Two[6,9] studies used a retrospective analysis and 1 study[8] derived their score from the previous bleeding score available in AF, while a retrospective study design was used in 1[12] VTE study and 1 mixed population study.[15]

Most studies in AF patients had follow-up for at least 1 year except the first score developed by Shiremen et al[9] which followed their patients for the first 90 days following hospital discharge after AF diagnosis. In contrast, bleeding scores derived from VTE cohorts usually followed up patients for 3 months, as the duration of treatment of DVT/PE with warfarin is typically between 3-12 months depending on the type of VTE.[19] All studies derived their risk score using bleeding risk factors from large cohorts of patients ranging from 3456[7] to almost 20,000[9] patients, apart from 2 studies, by Kuijer and Landefield et al. which only included 241 and 556 patients, respectively.[12,15]

All bleeding risk scores stratified patients into 3 categories of bleeding risk (low, intermediate and high) except for the HAS-BLED score which initially categorised bleeding risk as high (score ≥3) and low-moderate risk (0-2)[1] and IMPROVE[10] which categorized scores as ≥7 (increased risk of bleeding) and <7. These bleeding risk scores showed major bleeding rates ranging from 0.1%-3% in the low risk group and 4.9%-30% in the high risk group in the validation cohorts. **(Table 4)**

In terms of VTE prophylaxis, the most recent bleeding risk score developed to assess bleeding risks is the IMPROVE,[10] and is perhaps the most comprehensive score by including more predictors of major bleeding (10 predictors), compared to the scores by Ruiz-Gimenez et al[11] (6 predictors) and Kuijer et al[12] (3 predictors).

The earliest bleeding score developed by Landefeld et al[15] in 1989 derived 5 predictive factors of major bleeding in a mixed indication population. One of the original risk factors was AF but this was later removed when the score was validated, as its association with major bleeding was no longer significant in the validation cohort. Diabetes mellitus was substituted instead of AF as a new predictor of major bleeding.

The ability of the bleeding risk scores to predict bleeding risk has been validated both in cohorts to similar to ones where the score was derived (4 studies)[6,7,9,11] and in independent validation cohorts (6 studies).[4,5,8,10,12,20] In the validation and comparison study by Hijazi et al,[4] the ABC score statistically outperformed the HAS-BLED and ORBIT scores in predicting major bleeding in both the derivation cohort

[0·68 (95% CI 0·66–0·70) vs. 0·61 (0·59–0·63) vs. 0·65 (0·62–0·67), respectively; ABC-bleeding vs. HAS-BLED p<0·0001 and ABC-bleeding vs. ORBIT p=0·0008] and the external validation cohort [0·71 (95% CI 0·68–0·73) vs. 0·62 (0·59–0·64) for HAS-BLED vs. 0·68 (0·65–0·70) for ORBIT; ABC-bleeding vs. HAS-BLED p<0·0001 and ABC-bleeding vs. ORBIT p=0·0016].[4] Although the ABC score performed better than the HAS-BLED and ORBIT scores in this report, the complexity of the algorithm and inclusion of biomarkers which are not routinely performed in daily clinical practice, may make it difficult and more costly, for physicians to apply routinely.

One recent meta-analysis[21] compared the diagnostic accuracy between HAS-BLED and $HEMORR_2HAGES$, ATRIA, $CHADS_2$ or CHA_2DS_2-VASc scores in anticoagulated patients with AF. The findings revealed that the HAS-BLED score performed better than the $HEMORR_2HAGES$ and ATRIA bleeding scores, as well as being superior to $CHADS_2$ or CHA_2DS_2-VASc in predicting bleeding. Despite having better performance when compared to $HEMORR_2HAGES$, ATRIA and ORBIT, an additional advantage of the HAS-BLED score over the other five bleeding scores is the inclusion of quality of anticoagulation control (the 'L' acronym for labile INR or poor TTR<65%). Time in therapeutic (TTR) is a reflection of anticoagulation control in patients taking a VKA; a target TTR of ≥70% is optimal for efficacy and safety.[22]

In a post-hoc analysis evaluating the performance of HAS-BLED, ATRIA and ORBIT bleeding risk scores in the AMADEUS trial,[23] TTR was strongly correlated with clinically relevant bleeding events in patients using the ATRIA and ORBIT score, thus demonstrating that incorporating TTR in bleeding scores improves their ability to predict future bleeding events. Another comparison of four bleeding risk scores (HAS-BLED, ORBIT, ATRIA and $HEMORR_2HAGES$) in the SPORTIF cohort[24] also investigated whether the addition of 'labile INR' (TTR<65%) improved bleeding risk prediction (with the exception of the HAS-BLED score which already contains labile INR). Addition of 'labile INR' to the ORBIT, ATRIA and $HEMORR_2HAGES$ bleeding risk scores, significantly improved the predictive performance of each

score for major bleeding [integrated discriminatory improvement (IDI) 0.0023, p=0.0092 vs. IDI 0.0020, p=0.00014 vs. IDI 0.0015, p=0.0016, respectively].[24]

Apostolakis et al[25] compared the predictive performance of HAS-BLED with HEMORR$_2$HAGES and ATRIA in the AMADEUS trial and demonstrated that the HAS-BLED score performed better than HEMORR$_2$HAGES and ATRIA score in predicting any clinically relevant bleeding, with only the HAS-BLED score demonstrating significant improvement for intracranial hemorrhage.[25] In another ancillary analysis of the same trial,[26] the HAS-BLED score performed better than the ORBIT score in predicting any clinically relevant bleed in a non-oral anticoagulant (idraparinux).[26]

More recently the predictive ability of the HAS-BLED score was also investigated in patients receiving NOAC therapy, with rivaroxaban, in a small retrospective case-control study;[27] the HAS-BLED score demonstrated modest diagnostic ability to predict major bleeding events although this was not statistically significant (c statistics=0.68; p=0.07).[27] Analyses have demonstrated that the HAS-BLED score not only performs well in predicting bleeding events in VKA treated patients with AF, it can also be used to predict bleeding events in non-VKA treated patients which is very useful as more AF patients are being treated with NOACs. [27]

Whereas in the VTE cohorts, only the IMPROVE score has been shown to have good predictive ability for major [ROC 0.67 (95% CI, 0.57-0.77; p=0.008)] and clinically important bleeding [ROC 0.64 (95CI, 0.55-0.73; p=0.0080] at 14 days when validated by Hostler et al in a cohort of 1688 hospitalised patients.[28]

In conclusion, balancing individual risk of thromboembolic events and bleeding is complex but maximising the benefit of OAC while minimising bleeding risk, resulting in a net clinical benefit, should be undertaken in all patients receiving OAC. As reviewed here, there are many clinical prediction tools to assess bleeding risk prior to starting OAC for either stroke prevention in AF or treatment of VTE, which should be used in clinical practice to identify and manage modifiable risk factors.

Acknowledgments: None

Declaration of Interest

HZ: Received funding from Malaysian Ministry of Education and Universiti Teknologi MARA for her PhD study.

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo

DAL: Investigator-initiated educational grants from Boehringer Ingelheim and Bristol Myers Squibb, speaker fees from Boehringer Ingelheim, Bayer, Bristol Myers Squibb, and Pfizer, consulting fees from Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer, and non-financial support from Boehringer Ingelheim and Bristol Myers Squibb, outside the submitted work.

Word count: 2013

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Table 1: Risk factors for bleeding included in each bleeding risk score

Risk factor	ABC[4]	ORBIT[5]	ATRIA[6]	HAS-BLED[7]	HEMORR$_2$HAGES[8]	Shireman[9]	IMPROVE[10]	Ruiz-Gimenez[11]	Kuijer[12]	OBRI[15]
Age ≥85							✓			
Age≥75		✓	✓		✓			✓		
Age≥70						✓				
Age≥65				✓						✓
Age ≥60									✓	
Age≥50	✓									
Biomarkers	✓									
Previous/remote bleed	✓	✓	✓	✓	✓	✓		✓		✓
Recent bleed						✓				
Anaemia		✓	✓		✓	✓		✓		✓
Renal disease		✓	✓	✓	✓		✓	✓		✓
Liver disease				✓	✓		✓			
Hypertension			✓	✓	✓					
Myocardial infarction										✓
Diabetes						✓				✓
Malignancy					✓		✓	✓	✓	
Stroke				✓	✓					✓
Combined antiplatelet therapy		✓		✓		✓				
Labile INR				✓						
Alcohol excess				✓	✓	✓				
Excessive fall risk					✓					
Genetic factors					✓					

Active gastro-duodenal ulcer							✓			
Bleeding 3 months before admission							✓			
Reduced platelet count					✓		✓			
ICU/CCU							✓			
Central venous catheter							✓			
Rheumatic disease							✓			
Male sex								✓		
Female sex						✓			✓	
Clinically overt PE								✓		
Total no. of risk factors/score	**3**	**5**	**5**	**9**	**12**	**8**	**10**	**6**	**3**	**7**

CCU = coronary care unit; ICU = intensive coronary care unit; INR = international normalised ratio; PE = pulmonary embolism

Table 2: Baseline patient characteristics of the derivation cohorts for each bleeding risk score

Patients, %	ABC[4]	ORBIT[5]†	ATRIA[6]†	HAS-BLED[7]†	HEMORR$_2$HAGES[8]‡	Shireman[9]	IMPROVE[10]	Ruiz-Gimenez[11]	Kuijer[12]	OBRI[15]
Number of patients	14,537	581	307	53	1604	19,875	10,866	314	241	556
Mean age (SD)/median (IQR)	70 (19-97)	78 (71–83)	-	73 (10)	80.2	88% ≥70 years	68.1 (51.8-78.9)	66 (17)	63 (17)	61 (14)
Sex (female)	36	46.1	37.4	53	57	52.5	50.6	45	46	54
Ethnicity White	-	91.6	86.2	-	-	-	-	-	-	93
History/ diagnosis of cancer	-	30.8	18.0	-	4.8	2.5	10.7	35	24	-
Anaemia/abnormal Hb/Hct	-	57.5	18.8	-	8.5	7.5	-	56	-	-
Hypertension	87	89.3	64.7	74	0.4	72	38.7	-	-	-
Diabetes	25	33.7	22.1	23	-	29.6	-	-	-	8
CHF	31	44.9	-	45	-	59.8	10.8	7.6	-	-
MI	13	20.5	0.5	29**	-	68.5**	13	-	-	4
Prior stroke	19	13.1	17.4	12	37.2	32.1	-	-	-	12
GI bleed	-	15.5	12.1	17§	-	11.9	-	5.4	-	10
eGFR 60ml/min	74.1 ml/min	48.4	5.9 ¶	19‖	-	0.6 #	11.0¶	-	-	18
Antiplatelet	-	49.1	0.9	-	-	22.3	24.6	14	-	-
Warfarin	-	95	-	-	42.3	28.7	1.3*	-	-	-
NOACs	-	5.2	-	-	-	-	-	-	-	-

CAD = coronary artery disease; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; Hb = hemoglobin; Hct = hematocrit; IQR = interquartile range; MI = myocardial infarction; NOACs = non-vitamin K antagonist oral anticoagulant; SD = standard deviation *anticoagulant discontinued; †population experiencing major bleed only; ‡ warfarin users only; §major bleed; ‖ renal failure; ¶<30ml/min; #hepatic/renal failure; **CAD; - not reported

Table 3: Characteristics of the derivation and validation cohorts for each of the bleeding risk scores

			Derivation cohort				Validation cohort				
Risk score	Year	Country	Indication for OAC	Study design	Subjects	Follow-up	Indication for OAC	Study design	Subjects	Follow-up	Major bleed definition
ABC[4]	2016	Sweden	AF	Prospective	14,537	1.7 years†	AF	Prospective	8468	1.9†	ISTH
ORBIT[5]	2015	USA	AF	Prospective	7411	2 years	AF	Prospective	14,264	1.9†	ISTH
ATRIA[6]	2011	USA	AF	Retrospective	6123	6 years	AF	Retrospective	3063	6 years	ISTH
HAS-BLED[7]	2010	Europe	AF	Prospective	3456	1 year	AF	Prospective	3071	1 year	ISTH
$HEMORR_2HAGES$[8]	2006	USA					AF	Retrospective	3791	3 years	Hospitalisation for bleeding
Shireman[9]	2006	USA	AF	Retrospective	19,875	3 mth	AF	Retrospective	6470	3 mth	Hospitalisation for GI bleed or ICH
IMPROVE[10,28]	2011	USA	VTE	Retrospective or prospective	10,866	3 mth	VTE	Prospective	1668	18 mth	ISTH
Ruiz-Gimenez[11]	2008	Spain	VTE	Prospective	13,057	3 mth	VTE	Prospective	6572	3 mth	ISTH
Kuijer[12]	1999	The Netherlands	VTE	Retrospective	241	3 mth	VTE	Retrospective	780	3 mth	ISTH
OBRI[15,20]	1989	USA	Mixed‡	Retrospective	556	48 mth	Mixed‡	Prospective	264	48 mth	ISTH

AF = atrial fibrillation; DVT = deep vein thrombosis; GI = gastrointestinal; ICH = intracranial haemorrhage; ISTH = International Society of Thrombosis and Haemostasis; mth = months; PE = pulmonary embolism; TE = thromboembolism; TIA = transient ischaemic attack; VHD = valvalur heart disease; VTE = venous thromboembolism, valvular heart surgery, mitral valve disease, AF, stroke, transient ischemic attack (TIA), pulmonary embolism (PE), deep vein thrombosis (DVT), and other thromboembolism

†median; ‡mixed indication included valvular heart disease, AF, stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism and other thromboembolism

Table 4: Risk factors, risk categories and bleeding events in the validation cohorts

Risk score	Risk factors (score for each factor)	Risk categories			Bleeding events in validation cohort (per 100 patient yrs)		
		Low	Intermediate	High	Low	Intermediate	High
ABC[4]	Age(†); Biomarkers (†) (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, & Hb); Previous bleed (†)	<1%	1-2%	>3%	0.62	1.67	4.87
ORBIT[5]	Age ≥75 yrs (1); ↓Hb/Hct/anemia (2); Bleeding history (2); ↓ renal function (1); APT (1)	0-2	3	≥4	2.4*	4.7	8.1
ATRIA[6]	Anemia (3); Severe renal disease (3); Age ≥75 yrs (2); Prior bleed (1); Hypertension (1)	0-3	4	5-10	0.83	2.41	5.32
HAS-BLED[7]	↑SBP (1); Severe renal/hepatic disease (1 each); Stroke (1);Bleeding (1); Labile INR (1); Age >65 yrs (1); APT/NSAIDs (1); Alcohol excess (1)	0-1	2	≥3	1.02-1.13	1.88	≥3.74
$HEMORR_2HAGES$[8]	Hepatic/renal disease (1); Ethanol abuse (1); Malignancy; Age >75 yrs (1); ↓Plt (1); Re-bleeding risk (2); ↑BP (1); Anemia (1); Genetic factors (1); ↑ falls risk (1); Stroke (1)	0-1	2-3	≥4	1.9-2.5	5.3-8.4	10.4-12.3
Shireman et al[9]	Age ≥70 years (0.49); Female (0.31); Previous bleed (0.58); Recent bleed (0.62); Alcohol/drug abuse (0.71); DM (0.27); Anemia (0.86); APT (0.32)	≤1.07	>1.07/ <2.19	≥2.19	0.9% [a]	2.0% [a]	5.4% [a]
IMPROVE[10,28]	Active GI ulcer (4.5); Recent bleed (4); ↓Plt (4); Age ≥75 yrs (3.5); Hepatic/renal failure (2.5 each); ICU/CCU admission (2.5); CV catheter (2); Rheumatic disease (2); current cancer (2); Male (1)	<7	-	≥7	2.7%‡		6.5%‡
Ruiz-Gimenez et al [11]	Recent major bleed (2); ↑Creat (1.5); Anemia (1.5); Cancer (1); PE (1); Age >75 yrs (1)	0	1-4	>4	0.1%[a]	2.8% [a]	6.2% [a]
Kuijer et al [12]	Age≥60 yrs (1.6); Female (1.3); Malignancy (2.2)	0	1-3	>3	0.6% [a]	2% [a]	7% [a]
OBRI [15,20]	Age≥65 yrs (1); Previous stroke (1); Previous GI bleed (1); Recent MI/ anemia/DM/↑ creat (1)	0	1-2	3-4	3% [b]	8% [b]	30% [b]

APT = antiplatelet therapy; BP = blood pressure; CCU = coronary care unit; creat = creatinine; cTnT-hs = Troponin T; CV = central venous; DM = diabetes mellitus; GDF-15 = growth differentiation factor-15; GI = gastrointestinal; Hb = haemoglobin; Hct = hematocrit; ICU = intensive care unit; INR = international normalised ratio; MI = myocardial infarction; PE: pulmonary embolism; Plt = platelet count or function; SBP = systolic blood pressure; yrs = years

* bleeding event in original derivation cohort; [a] at 3 months; [b] at 12 months; ↓ reduced/decreased; ↑ elevated/increased; † score for each variable in ABC score is based on a nonogram (see reference[4]); ‡ clinically important bleeding: sum of major bleed and clinically relevant non-major