Veritsuse riski hindamise meetod

Kliiniline küsimus

Kas veritsusriski hindamiseks tuleks KVA patsientidel kasutada HASBLED skoori vs kliiniline hinnang/vs teised teadaolevad skoorid?

Olulised tulemusnäitajad

Surm, ajuinfarkt, trombemboolia, oluline verejooks, elukvaliteet, koljusisene verejooks, südame löögisageduse eesmärkväärtuse (nt ≤100 x/min) saavutamine, tõsine kõrvaltoime.

Mõõdukalt olulised: hospitaliseerimine, KVA taasteke (sek preventsioonil), ravi katkestama sundiv kõrvaltoime, südamepuudulikkus, aeg KVA esimese taastekkeni, siinusrütmi taastumine (kardioversioonil), siinusrütmi püsimine 12 kuud.

Kliinilise tõenduse kokkuvõte

Põhiline informatsioon tuleneb NICE-i ravijuhendi (2014) koostamise käigus tehtud ülevaatest, mis hõlmas 17 uuringut. Põhiline tulemusnäitaja oli riski(tiheduste) suhe (*hazard ratio, HR*) oluliseks veritsuseks, hinnates erinevate veritsusriski skooringute kategooriaid eraldi. Uuringutes toodi välja riskitiheduste suhte mediaan (*median hazard ratio*) ja usaldusvahemik uuringutes, millel oli üle 100 veritsusepisoodi, et vähendada nihet (*bias*) tulemustes[1].

Iga uuringu kohta raporteeriti ROC-kõvera alune pindala (c-statistikuna). ROC-kõvera alune pindala kirjeldab antud kontekstis testi prognostilist täpsust eristada erinevates kategooriates olevate patsientide olulise veritsusriski tekke tõenäosust.

NICE kasutas järgnevaid kriteeriume ROC-kõvera aluse pindala kohta:

<0,5 – halvem kui juhus

0,5-0,6 – kehv test

0,61-0,7 – puudulik test

0,71-0,80 - rahuldav test

0,81 – 0,90 – hea test

0,91-1,0 – väga hea või perfektne test

ATRIA		HAS-BLED		HEMORR$_2$HAGES	
Anaemia	3	Hypertension	1	Hepatic or Renal disease	1 1
Severe renal disease	3	Abnormal Renal or Liver function	1 1	Ethanol abuse	1
Age ≥75 yrs	2	Stroke	1	Malignancy	1
Any prior hemorrhage	1	Bleeding	1	Older Age (>75 yrs)	1
Hypertension[3]	1	Labile INR	1	Reduced platelet number or function	1
		Elderly (>65 yrs)	1	Rebleeding	2
		Drugs or Alcohol	1 1	Hypertension	1
				Anaemia	1
				Genetic factors	1
				Excessive fall risk	1
				Stroke	1

Singer et al. Ann Intern Med. 2009; 151: 297-305.
Gage et al Am Heart J. 2006; 151: 713-9.
Pisters et al Chest. 2010; 138: 1093-100.

Keskmise kvaliteediga tõendus 6-st uuringust näitas c-statistikut HAS-BLED skoorile vahemikus 0,6-0,795, mis jääb puuduliku ja rahuldava kvaliteediga testi hulka.

Hea kvaliteediga tõendus ühest uuringust näitas C-statistikut ATRIA skoorile 0,6.

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[1] Lisaks on uuritud ORBIT skoori (1 punkt: vanus >75a, eGFR <60 mL/min/1.73 m2, antiagregandi kasutamine, 2 punkti: verejooksu anamnees, aneemia või hemoglobiin <13 mg/dL meestel ja <12 mg/dL naistel). Ka see ei ületanud HAS-BLED-i. Senoo K et al. The American Journal of Medicine (2016) 129, 600-607.
Viimatisena on lisandunud biomarkereid kaasav ABC skoor, mille kõik komponendid (*growth differentiation factor-15 (GDF-15)* ei ole rutiinina laboris määratavad. Hijazi Z jt. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet 2016; 387:2302–2311.

Keskmise kvaliteediga tõendus 4-st uuringust näitas C-statistiku HEMORR2HAGES skoori kohta vahemikus 0,59-0,782.

Hea kvaliteediga tõendus 2-st uuringust raporteeris C-statistiku CHAD2 skoorile 0,51-0,59.

Mediaan riskitiheduste suhe (*median hazard ratio*) veritsuseks võrreldes kõrge riski kategooriat madala riski kategooriaga oli 3,57 HAS-BLEDi korral (keskmine tõenduse kvaliteet), 2,90 HEMORR2HAGES skoori kohta (madal tõenduse kvaliteet) ja 2,48 ATRIA skoori kohta (hea tõenduse kvaliteet). Need võrdlused olid tehtud ühe uuringupatsientide grupi kohta ja leidsid, et HAS-BLED skoor oli kõige parem eristamaks erineva riski gruppe.

Teiste ravijuhendite soovitused samal teemal

AHA 2014 juhend mainib erinevad riskiskooringu võimalused (HAS-BLED, HAEMORR2HAGES ja ATRIA), kuid kuna nende prognostiline täpsus on halb (kõigil C-indeks < 0,70), siis ei anna soovitusi nende kasutamiseks.

Kanada ravijuhend mainib erinevad riskiskooringu võimalused (HAS-BLED, HAEMORR2HAGES ja ATRIA), kuid soovitab nendest kasutada praktilistel kaalutlustel HAS-BLED skoori, kuna see on paremini valideeritud (ka vanemaealistel) kui ATRIA ja on kliinilises rutiinis oluliselt lihtsamini kasutatav kui HAEMORR2HAGES.

ESC 2016 ravijuhend mainib erinevad veritsusriski skoorid ja nendib, et nende kasutamine on soovitatav (IIa, B), et tuvastada muudetavaid veritsusriski faktoreid.

NICE ravijuhend hindab põhjalikult 3 skoori (HAS-BLED, HAEMORR2HAGES ja ATRIA) efektiivsust ja kliinilist kasutust. Kõik on kehvad eristamaks kõrge veritsusriskiga patsiente madalama riskida patsientidest, kuid HAS-BLED oli teistest marginaalselt parem. Lisaks on HAS-BLED lihtsalt kasutatav võrreldes teisega ja valideeritud ka mitte-varfariini kasutajatel ja mitte ainult valgel rassil. Põhiline kasu veritsusriski hindamisest tuleneb modifitseeritavate riskifaktorite tuvastamisest ja käsitlemisest ja HAS-BLED tuvastab neid kõige rohkem. Seetõttu soovitatakse kasutada HAS-BLED skooringut, pannes rõhku muudetavatele veritsusriski faktoritele.

Soome ravijuhend soovitab kasutada HAS-BLED riskiskoori veritsusriski hindamiseks.

Viited

1. *The management of atrial fibrillation. National Clinical Guideline Centre, 2014*
2. *Apostolakis S1, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study.J Am Coll Cardiol. 2012 Aug 28;60(9):861-7.*
3. *Senoo K1, Proietti M1, Lane DA1, Lip GY2. Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin. Am J Med. 2016 Jun;129(6):600-7.*

Kokkuvõte uuringuist tabelina

Table 35: Clinical evidence profile: Bleeding risk scores

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
Hazard ratio for major bleeding (categorical variables) – HAS-BLED score[286,288,337]										
HAS-BLED ≥3vs<3										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	High: 158/1254 (12.6%) Moderate and low: 392/5902 (6.6%)	53 more per 1000 (from 37 more to 70 more)	HR[95% CI]: 1.85 [1.60-2.14]	HIGH
HAS-BLED 1-2 versus <1										
3	Cohort studies	serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Moderate (score 2): 721/14933 (4.8%) Low (score 0-1): 377/15570 (2.4%)	25 more per 1000 (from 19 more to 31 more)	Median HR[95% CI]: 2.07 [1.83-2.34] Range of HR: 2.00-4.31	MODERATE
HAS-BLED ≥3vs<1										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
3	Cohort studies	serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	≥3: 158/1254 (12.6%) <1: 49/1282 (3.8%)	91 more per 1000 (from 57 more to 136 more)	Median HR[95% CI]: 3.57 [2.59-4.92] Range of HR: 3.00-8.56	MODERATE
Hazard ratio for major bleeding (categorical variables) – HEMORR$_2$HAGES score[286,288,337]										
HEM ≥2 versus <2										
1	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 1.80 [1.49-2.17]	MODERATE
HEM mod versus low										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
3	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 592/21185 (2.8%) Moderate: 1006/18713 (5.4%) High: 453/4873 (9.3%)	28 more per 1000 (from 23 more to 34 more)	Median HR[95% CI]: 2.04 [1.85-2.26] Range: 1.85-2.19	MODERATE
HEM high versus low										
3	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	Serious imprecision [c]	none	MEDIAN - LIP 2012: NR Olesen 2011: Low: 592/21185 (2.8%) High: 453/4873 (9.3%) Lip 2011*: High: 2/99 (2%) Low: 81/2694 (3.0%)	*55 more per 1000 (from 15 more to 127 more)	Median HR[95% CI]: 2.90 [1.5-5.61] Range: 0.75-3.87	LOW
Hazard ratio for major bleeding (categorical variables) – HEMORR$_2$HAGES score[286]										
ARIA ≥4 versus <4										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 1.61 [1.41-1.84]	HIGH
ATRIA mod versus low										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 2.09 [1.46-2.99]	HIGH
ATRIA high versus low										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 2.48 [1.88-3.27]	HIGH
C-statistics[24,154,286,288,337,382]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
HAS-BLED										
6	Cohort studies	serious limitations [a, d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Lip 2012: High: 158/1254 (12.6%) Moderate: 343/4620 (7.4%) Low: 49/1282 (3.8%)	NR	Median c-statistic [95% CI]: 0.61 [0.59-0.62] 0.61 [0.58-0.65] Range of HR: 0.60-0.795	MODERATE
ATRIA										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	c-statistic [95% CI]: 0.60 [0.56-0.63]	HIGH
$HEMORR_2HAGES$										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
4	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Lip 2011: High: 2/99 (2%) Moderate: 53/872 (6.1%) Low: 81/2694 (3.0%) Friberg 2012: NR	NR	Median statistic [95% CI]: 0.61 [0.56-0.65] 0.63 [0.61-0.64] Range of HR: 0.59-0.782	MODERATE
$CHADS_2$										
2	Cohort	no serious limitations	no serious inconsistency	no serious indirectness	No serious imprecision	none	Apostolakis 2013: Low: 7/54 (13%) Moderate: 165/1540 (10.7%) High: 79/699 (11.3%)	NR	C-statistic [95% CI]: 0.51 (0.47-0.55) 0.59 (0.56-0.62)	HIGH

a. Studies have a serious risk of bias as one or more of the studies has missing information on the score (labile INR)
b. Studies have a serious risk of bias as one or more of the studies have missing information on the score (genetic information)
c. Confidence interval crossed two MIDs (0.75 and 1.25) in one of the three studies
d. Studies have a serious risk of bias as one of the studies used population without alcohol abuse or previous major bleeding which are components of the score

I.5 Bleeding risk scores

Figure 56: Hazard ratio for bleeding by risk score

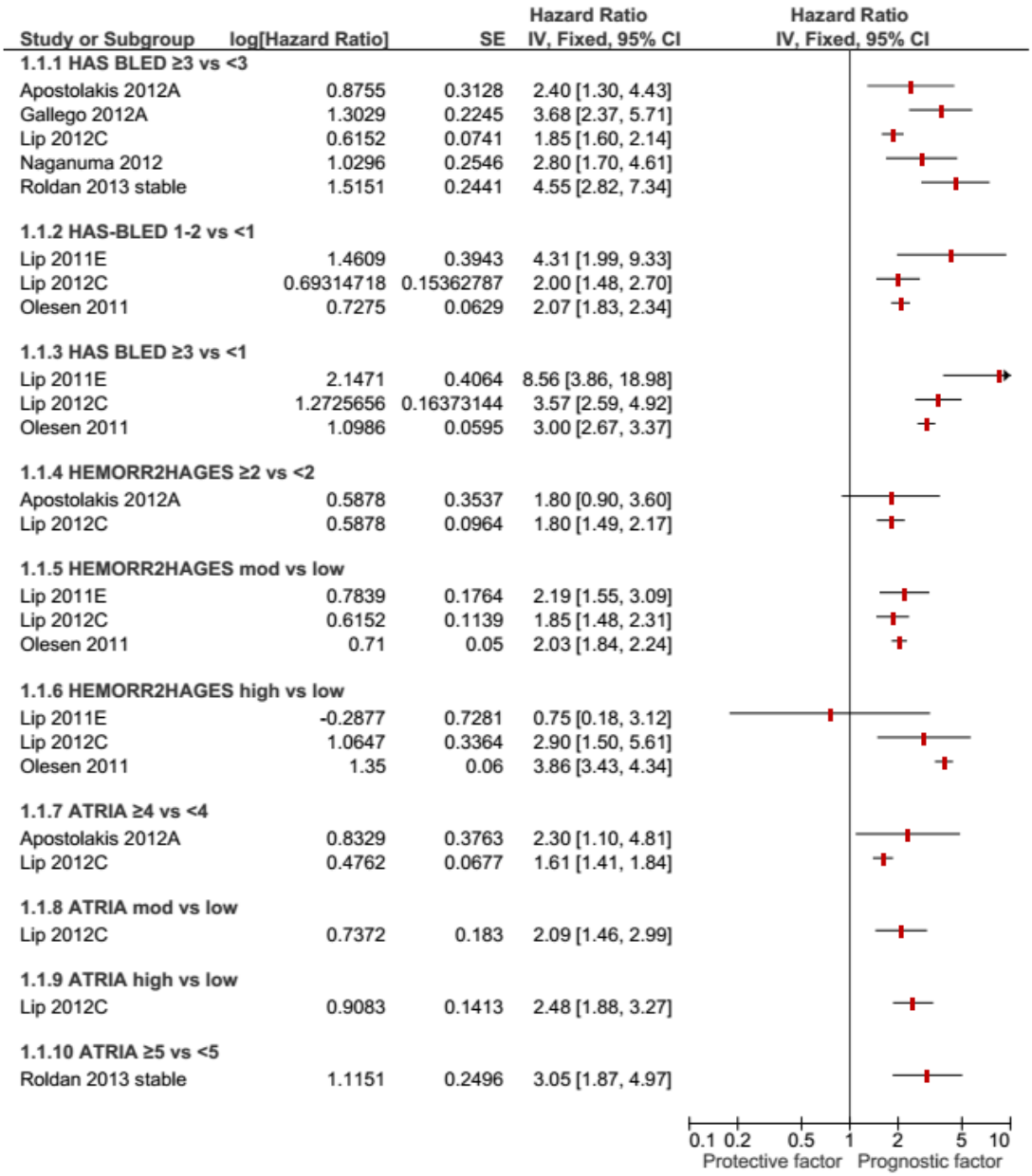
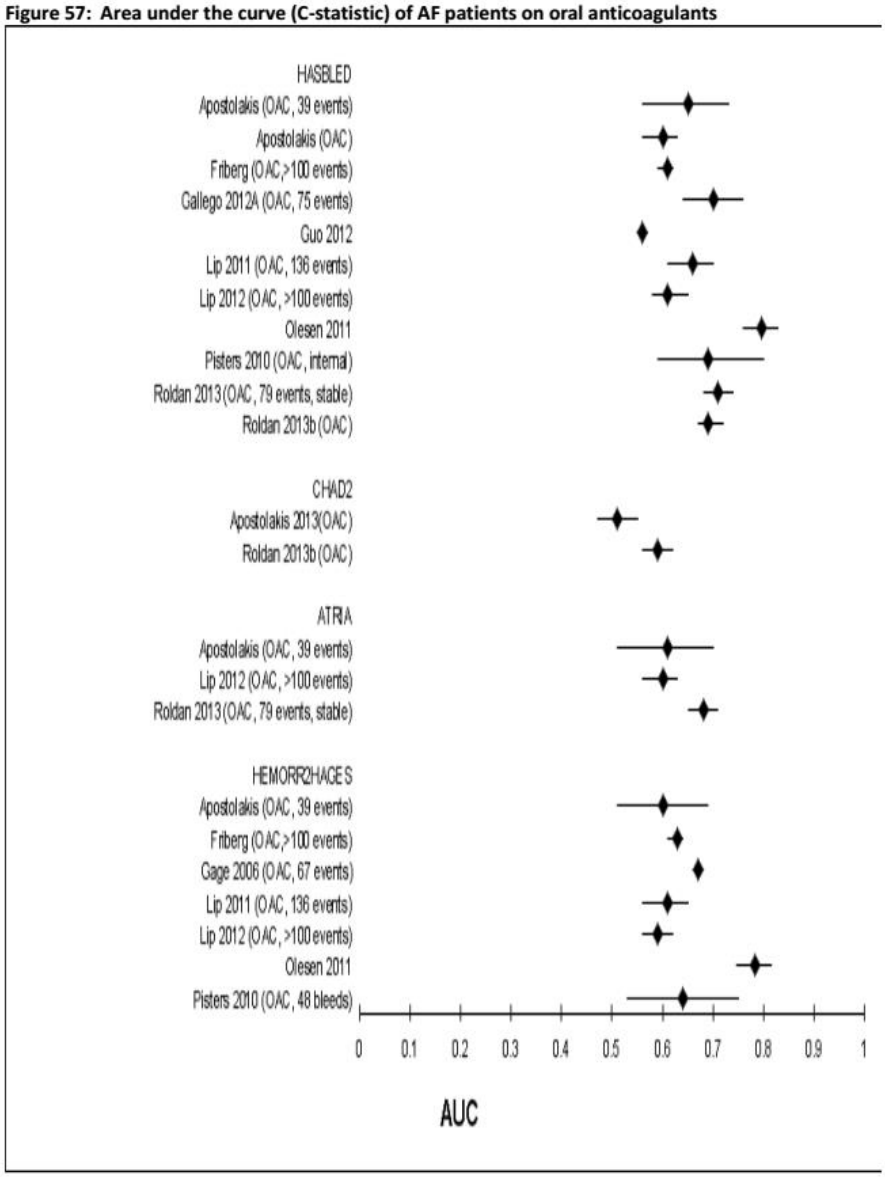


Figure 57: Area under the curve (C-statistic) of AF patients on oral anticoagulants



C-statistics - on oral anticoagulants			
Study	**Lower CI**	**Point estimate**	**Upper CI**
HASBLED			
Apostolakis (OAC, 39 events)	0.56	0.65	0.73
Apostolakis (OAC)	0.56	0.6	0.63
Friberg (OAC,>100 events)	0.59	0.61	0.62
Gallego 2012A (OAC, 75 events)	0.64	0.7	0.76
Guo 2012		0.56	
Lip 2011 (OAC, 136 events)	0.61	0.66	0.7
Lip 2012 (OAC, >100 events)	0.58	0.61	0.65
Olesen 2011	0.759	0.795	0.829
Pisters 2010 (OAC, internal)	0.59	0.69	0.8
Roldan 2013 (OAC, 79 events, stable)	0.68	0.71	0.74
Roldan 2013b (OAC)	0.67	0.69	0.72
CHAD2			
Apostolakis 2013(OAC)	0.47	0.51	0.55
Roldan 2013b (OAC)	0.56	0.59	0.62
ATRIA			
Apostolakis (OAC, 39 events)	0.51	0.61	0.7
Lip 2012 (OAC, >100 events)	0.56	0.6	0.63
Roldan 2013 (OAC, 79 events, stable)	0.65	0.68	0.71
HEMORR2HAGES			
Apostolakis (OAC, 39 events)	0.51	0.6	0.69
Friberg (OAC,>100 events)	0.61	0.63	0.64
Gage 2006 (OAC, 67 events)	0.668042	0.67	0.671958
Lip 2011 (OAC, 136 events)	0.56	0.61	0.65
Lip 2012 (OAC, >100 events)	0.56	0.59	0.62
Olesen 2011	0.745	0.782	0.816
Pisters 2010 (OAC, 48 bleeds)	0.53	0.64	0.75

Table 34: Summary of studies included in the review

Study	Bleeding risk score	Population	Outcomes	Comments
Apostolakis 2012A27 Retrospective cohort (n=2292)	HAS-BLED HEMORR2HAGES	AF, anticoagulation: all on warfarin. External validation study; Non-warfarin anticoagulation validation	Major bleeding (39 events) Hazard Ratio (HR)- Cox AUC Calibration Net Reclassification Index (NRI)	History of bleeding excluded; no genetic data
Apostolakis 201324 Post hoc from trial AMADEUS	HAS-BLED CHADS2	AF undergoing anticoagulation	AUC NRI	History of bleeding and alcohol abuse excluded; these are criteria of the HAS-BLED score
Fang 2011143 Internal validation for ATRIA Retorpsective cohort	Atria	Non valvular, non-transient AF	Major bleeding (307 events) Time varying covariates: AUC, NRI,	Duration of follow up not reported. Some baseline details not reported (age and sex)
Friberg 2012B154 Retrospectiv	HAS-BLED HEMORR2HAGES	AF (according to ICD-10, code 1489); warfarin	Major bleeding (defined as all intracranial bleeds, gastro-intestinal bleeds and	Labile INR data not available so ignored in HAS-BLED;

Study	Bleeding risk score	Population	Outcomes	Comments
e cohort (registry data); external validation (n=68,307 on warfarin at baseline)		and non-warfarin separately	anaemia) 5810 events (195 in those not on OAC) AUC	genetic factors not available so ignored in HEMORR2HAGES
Gage 2006162 Retrospective registry data (Medicare) (n=1604 on warfarin)	HEMORR2HAGES	Patients with AF on warfarin (subset)	Major bleeding (defined by hospitalisation)30 events (aspirin), 67 (warfarin), AUC Rates	
Gallego 2012A166 Prospective cohort (n=965)	HAS-BLED ≥3 versus <3 (assumed lower group)	Consecutive patients with permanent/paroxysmal non-valvular AF, all on anticoagulants, but with INR between 2.0 and 3.0 during previous 6 months. Patients from outpatient clinic	Major bleeding (ISTH criteria, decrease of 20g/l) 75 events HR(Cox) AUC	Risk in lowest group not stated
Guo 2012183	HAS-BLED	Patients with AF	AUC	Reported AUC for CHADS2 and CHA2DS2-VASc for stroke risk
Lip 2012C286 Retrospective cohort (n=7156)	HAS-BLED ≥3 versus 1-2 versus <1 Atria HEMORR2HAGES	Non-valvular AF or atrial flutter. With and without Vitamin K Antagonist (VKA) (reported separately for AUC)	Major bleeding with ≥20g/l decrease (n=550; unclear for VKA HR AUC Lowest risk group: 49/1282 (3.8%)	Genetic information not available
Lip 2011E288 Retrospective cohort study from2 RCTs (n=7329; 3665 on warfarin)	HAS-BLED ≥3 versus 1-2 versus <1 (assumed) HEMORR2HAGES	Permanent/paroxysmal non-valvular AF, with at least 1 risk factor for stroke; randomised to ximelagatran versus warfarin. Reported separately for warfarin, warfarin	Major bleeding (fatal/clinically overt bleeding, with ≥20g/l decrease) (217 events; warfarin only 136) HR (warfarin only)	Genetic information not available

Study	Bleeding risk score	Population	Outcomes	Comments
		plus aspirin and VKA naïve at baseline		
Naganuma 2012318 Retrospective cohort (n=845)	HAS-BLED (≥3 versus 1-2) Validation	Non-valvular AF; patients >75 years; all on warfarin, with INR	Major bleeding (intracranial, intraocular, GI, hospital admission, blood transfusion) 36 events HR (Cox, possibly MV)	No details on imputation. Risk for 1-2 points: 7/346 (2.0%)
Oldgren 2011336 Retrospective cohort	CHADS2	AF with one documented risk factor for stroke.	None reported	Not a bleeding risk tool validation paper
Olesen 2011A339 Retrospective cohort (N=118584, n=44771 on anticoagulation)	HAS-BLED HEMORR2HAGES	Non-valvular AF with or without OAC	C-statistic HR for major bleeding (unadjusted cox proportional hazard analyses) 2051 bleeding events. Outcome was hospitalisation or death from major bleeding, including gastrointestinal bleeding, intracranial bleeding, bleeding from the urinary tract or airway bleeding.	Genetic and labile INR information not available
Pisters 2010360 Retrospective analysis (database)	HAS-BLED HEMORR2HAGES Appears to be derivation study for HAS-BLED; external validation HEMORR2HAGES	AF; results reported separately for anticoagulants alone, antiplatelet therapy alone, both and none	Major bleeding – hospitalisation and/or Hb decrease of >2g/l and/or blood transfusion 48 events only AUC only	Genetic data not available
Roldan 2011384 Prospective cohort; but baseline from outpatient database N=829	HAS-BLED	Permanent AF who were stabilised on oral anticoagulation therapy	HR (multivariate analysis) 68 bleeds	
Roldan 2013383 Prospective cohort; but baseline from	HAS-BLED ≥3 versus <3 Atria ≥5 versus <5	Consecutive patients with permanent/paroxysmal non-valvular AF, all on acenocoumarol,	79 haemorrhagic events HR (unadjusted) AUC NRI	Only stable warfarin and experienced patients included. Prognostic factors all available in

Study	Bleeding risk score	Population	Outcomes	Comments
outpatient database		but with INR between 2.0 and 3.0 during previous 6 months		database => collected retrospectively
Roldan 2013b382	HAS-BLED CHADS2	AF patients on anticoagulation	AUC HR (univariable)	Only patients with stable oral anticoagulation were included.
Seet 2013396 Prospective cohort; but baseline from retrospective outpatient database N=100	HAS-BLED HEMORR2HAGES	Ischaemic stroke patients with AF	41 major bleeding events C statistic (continuous outcome, no CIs) Major bleeding defined as fatal or clinically overt bleeding associated with either transfusion of 2 or more units of blood or greater than or equal to 20 g/L decrease in haemoglobin or bleeding involving a critical anatomic site. Intracranial haemorrhage was counted as major bleeding event.	Genetic information not available.