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Toward better risk stratification for stroke prevention in AF : Beyond the CHA₂DS₂VASc Score

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Declaration of Interests

- <u>Guideline membership/reviewing:</u> ESC Guidelines on Atrial Fibrillation 2010 and Focused Update 2012, 2020; ESC Guidelines on Heart Failure, 2012; American College of Chest Physicians Antithrombotic Therapy Guidelines for Atrial Fibrillation, 2012; NICE Guidelines on Atrial Fibrillation, 2006 and 2014; NICE Quality Standards on Atrial Fibrillation 2015; ESC Cardio-oncology Task Force, 2015; ESC Working Group on Thrombosis position documents (2011-). Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Chairman, 2018 CHEST guidelines from American College of Chest Physicians. Writing Group, 2021 Asia Pacific Heart Rhythm Society Guidelines on Stroke Prevention.
- <u>Steering Committees/trials</u>: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc.
- <u>Editorial Roles</u>: Editor-in-Chief (clinical), Thrombosis & Haemostasis; Associate Editor, Europace; Guest Editor, Circulation, American Heart Journal.
- <u>Consultant/Advisor/Speaker:</u>
 - Consultant and Speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No direct personal fees.

Stroke risk factors in patients with Atrial Fibrillation

Hindricks et al Eur Heart J 2020 doi:10.1093/eurheartj/ehaa612

Most commonly studied clinical risk factors (a systematic review) ³²⁴	Positive studies/All studies	Other clinical risk factors ³²⁵	Imaging biomarkers ^{291,326–328}	Blood/urine biomarkers ³²⁹⁻³³²
Stroke/TIA/systemic embolism	15/16	Impaired renal function/ CKD	Echocardiography	Cardiac troponin T and I Natriuretic peptides
Hypertension	11/20	OSA	LA dilatation	Cystatin C
Ageing (per decade)	9/13	HCM	Spontaneous contrast or	Proteinuria
Structural heart disease	9/13	Amyloidosis in degenerative cerebral and heart diseases	thrombus in LA Low LAA velocities	CrCl/eGFR CRP
Diabetes mellitus	9/14	Hyperlipidaemia	Complex aortic plaque	IL-6
Vascular disease	6/17	Smoking	Cerebral imaging	GDF-15
CHF/LV dysfunction	7/18	Metabolic syndrome ³³³	Small-vessel disease	D-dimer
Sex category (female)	8/22	Malignancy		D-differ

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GDF-15 = growth differentiation factor-15; IL-6 = interleukin 6; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

The CHA₂DS₂-VASc score

a) Risk fa	ctors for stroke and throm	boembolism in	non-valv	ular AF
Ϋ́	1ajor' risk factors	'Clinically releva	ant non-majo	or' risk factors
Previous strok	e, TIA or systemic embolism Age ≥ 75 years	Heart failure c systolic dysfur Hypertensi Female si Vas	or moderate t action (e.g. L) ion - Diabetes ex - Age 65-74 scular disease	to severe LV $V EF \leq 40\%$] mellitus 4 years
	Stroke risk factors		Score	
	<u>C</u> ongestive heart failure/L\	/ dysfunction	1	
	<u>Hypertension</u>		1	
	<u>A</u> ged ≥75 years		2	
	<u>D</u> iabetes mellitus		1	
	<u>S</u> troke/TIA/TE		2	
	<u>V</u> ascular disease [prior MI, or aortic plaque]	PAD,	1	
	<u>Ag</u> ed 65–74 years		1	Lip et al.
	<u>S</u> ex category [i.e. female g	ender]	1	2010;137

CHA₂DS₂-VASc Scores of Patients With AF ±Ischemic Stroke: Baseline, Follow-Up, Delta

Chao, Lip et al J Am Coll Cardiol. 2018;71(2):122–32.





Incident Co-Morbidities in AF Patients Initially with a CHA₂DS₂-VASc Score of 0 (Males) or 1 (Females): Implications for Reassessment of Stroke Risk in Initially 'Low-Risk' Patients

Chao .. Lip et al Thromb Haemost. 2019 Jul;119(7):1162-1170. .



- In 80% of patients who acquired a comorbidity (HF, hypertension, diabetes or vascular disease), the new condition occurred after 4.2 months of AF diagnosis.
- Time from incident comorbidity to ischaemic stroke was >4.4 months for 90% of patients suffering stroke.

3-4 months may be a reasonable time interval at which stroke risk should be re-assessed, so that OACs could be prescribed timely.

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Does chronic kidney disease improve predictive value of the CHADS₂ and CHA₂DS₂-VASc stroke stratification risk scores for AF?

> Roldan ... Lip Thromb Haemostat 2013 May 2;109(5):956-60.

Evaluating renal function in AF patients is important as CKD would confer a poor overall prognosis

Adding CKD to the CHADS₂ and CHA₂DS₂-VASc stroke risk scores did not independently add predictive information.

Stroke/systemic embolism	C-statistic (95% CI)	Ρ	Relative IDI	Ρ
CHADS ₂	0.650 (0.619-0.680)			
CHADS ₂ +CKD	0.636 (0.605-0.666)	0.442	0.7%	0.260
CHA2DS2-VASc	0.623 (0.592-0.654)			
CHA2DS2-VASc+CKD	0.612 (0.580-0.642)	0.451	0.3%	0.122
Thrombotic events	C-statistic (95% CI)	Ρ	Relative IDI	Ρ
CHADS ₂	0.628 (0.597-0.658)			
CHADS ₂ +CKD	0.629 (0.598-0.660)	0.917	0.3%	0.552
CHA2DS2-VASc	0.634 (0.603-0.664)			
CHA2DS2-VASc+CKD	0.636 (0.605-0.666)	0.908	0.7%	0.502
All cause death	C-statistic (95% CI)	Ρ	Relative IDI	Ρ
CHADS ₂	0.668 (0.638-0.698)			
CHADS ₂ +CKD	0.685 (0.655-0.714)	0.244	-2.5%	0.236
CHA2DS2-VASc	0.657 (0.627-0.687)			
CHA2DS2-VASc+CKD	0.672 (0.642-0.702)	0.224	-1.8%	0.290

CHADS₂: congestive heart failure, hypertension, age \geq 75, diabetes mellitus, and prior stroke or transient ischaemic attack; CHA₂DS₂-VASc: congestive heart failure, hypertension, age \geq 75, diabetes mellitus, prior stroke or transient ischaemic attack, vascular disease, age 65–74, female; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; CKD: we add 1 point for eGRF 30–60 and 2 points for eGFR<30.

Evaluating increased predictive ability of Chronic Kidney Disease (CKD) adding to clinical risk scores (CHADS₂ and CHA₂DS₂-VASc) using C-statistics and and IDI indexes.

N=978

Metabolically healthy obesity and cardiovascular events: A nationwide cohort study

Fauchier ... Lip, Fauchier. Diabetes Obes Metab. 2021 DOI: 10.1111/dom.14492

New-onset atrial fibrillation



'... individuals with MHO did not have a higher risk of myocardial infarction, ischaemic stroke or cardiovascular death than metabolically healthy individuals with no obesity. By contrast, they had a higher risk of new-onset HF and new-onset AF.'

Phenotypes defined by obesity and three metabolic abnormalities (diabetes, hypertension and hyperlipidaemia)

Metabolically healthy obesity and cardiovascular events: A nationwide cohort study

Fauchier ... Lip, Fauchier. Diabetes Obes Metab. 2021 DOI: 10.1111/dom.14492

Ischaemic stroke



Incidence (%/year)



'... individuals with MHO did not have a higher risk of myocardial infarction, ischaemic stroke or cardiovascular death than metabolically healthy individuals with no obesity. By contrast, they had a higher risk of new-onset HF and new-onset AF.'

Phenotypes defined by obesity and three metabolic abnormalities (diabetes, hypertension and hyperlipidaemia)

Adjusted HR

Risk of outcomes in AF patients with COPD vs. non-COPD.

Romiti .. Lip, Proietti. Eur Heart J 2021 doi:10.1093/eurheartj/ehab453



(A) All-cause death; (B) cardiovascular death;(C) ischemic stroke

Ew	150 81 97	Total 870 338	Events 992	Total 7250	Weight 8.2%	MH, Random, 95% 1.31 (1.09; 1.59)	CI N	4H, Rand	om, 95% Ci
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	97		00.00	20444	7.3%	1.46 [1.14; 1.89]			
		351	239	1461	7.0%	1.95 [1.49; 2.56]			
	232	1950	1037	10184	8.7%	1.97 [1.70; 2.29]			
	62	212	643	3833	6.5%	2.05 [1.51; 2.79]			
19	265	937	1096	7053	8.6%	2.14 [1.83, 2.51]			
	282	612	478	1740	8.2%	2.26 [1.86; 2.73]			
	46	273	55	766	5.2%	2,47 [1.63; 3.75]			
	38	339	126	2747	5.5%	2.63 [1.79; 3.85]			
	374	1604	833	0139	8.8%	2.67 [2.33; 3.06]			
1.53	61	227	214	1789	6.3%	2.70 [1.95; 3.75]			
54	4723	18607	67511	117549	9.6%	2.81 [2.71; 2.92]			
	34	185	133	1842	5.2%	2.89 [1.92; 4.37]			
	33	99	475	3552	5.0%	3.24 [2.11; 4.97]			-
		26604	1	194349	100.0%	2.22 [1.93; 2.55]	Ĕ.	_	+
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60 8	70	552	7250	11.8%	0.90	0.68; 1.18]			
6 2	12	109	3833	6.1%	1.00	(0.43; 2.29)	-		
44 6	112	332	1740	12.3%	1.30	11.05: 1.631			F
13 19	60	537	16184	12.4%	1.75	11.45:2.211			
30 2	27	135	1789	10.2%	1.87	11 22 2 851			-
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18 3	100	530	2747	0.010	2.04	12.07, 0.07			-
10 3	100	02	2747	0.075	2.91	[1.00, 0.03]			-
21 3	60	63	1042	9.5%	3.62	12.20, 5.10}			-
64	36		67520	100.0%	1.84	[1.39; 2.43]			•
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	14	212	276	3833	9.0%	0.91 10.52 1 501		-	
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	18	227	129	1789	9.4%	1.1110.66.1.851		_	
	6	185	51	1842	6.3%	1.18 (0.50, 2.78)			
	17	273	38	766	0.6%	1.27 10.71: 2.290		-	-
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	2	339	12	2747	3.1%	1.35 10.30; 6.071	8	_	
	. 8	99	134	3552	7.2%	2.24 [1.07; 4.71]			
	264	612	338	1740	12.2%	5.15 [2.58; 3.84]			
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Summary of biomarkers associated with atrial fibrillation and outcome measures.

Tidbury.. Lip. Expert Review of Precision Medicine and Drug Development 2020 https://doi.org/10.1080/23808993.2020.1 804864

	AF	Stroke	Bleeding	All-cause	
Biomarkers	incidence	risk	risk	mortality	Recurrence
NT-proBNP	*	*		*	
Troponins	*	*		*	
CRP	*				*
IL-6		*			
vWF		*			
D-dimer		*			
GDF-15			*	*	
TGF-β1	*				*
Galectin-3	*				*
sST2	*			*	*
LA size and	*	*			*
function					
LAA morphology		*			
Myocardial fibrosis (MRI-LGE)		*			*
4q25 locus	*	*			

* An association between the biomarker and outcome has been identified i clinical trials. AF, atrial fibrillation; CRP, C-reactive protein;GDF-15, growt differentiation factor-15; IL-6, interleukin-6; LA, left atrium; LAA, left atria appendage; MRI-LGE, magnetic resonance imaging-late enhanced gadoliniun NT-proBNP, N-terminal-pro B-type natriuretic peptide; sST2, soluble suppres sion of tumorigenicity 2; TGF-β1, transforming- growth factor-β1; vWF, vo Willebrand factor.

Additive Role of Plasma vWf Levels to Clinical Factors for Risk Stratification in AF

Lip et al Stroke 2006;37:2294-2300

Risk score level Annualized Rate (95% CI)		vWf Level	Annualized Rate (95% CI)
Ischemic stroke			
Birm, low	0 (0–0)	Low High	0 0
Birm, moderate	1.95 (1.17–2.92)	Low High	1.44 (0.69–2.48) 3.18 (1.44–5.59)
Birm, high	5.75 (3.68–8.28)	Low High	4.88 (2.51–8.04) 6.98 (3.59–11.5)
CHADS ₂ , low	0.65 (0.12–1.60)	Low High	0.54 (0.05–1.56) 1.09 (0.00–4.27)
CHADS ₂ , moderate	2.72 (1.76–3.89)	Low High	2.24 (1.22–3.56) 3.73 (1.85–6.26)
CHADS ₂ , high	7.03 (3.92–11.0)	Low High	5.68 (2.04–11.1) 8.37 (3.79–14.7)

Annualized Stroke Event Rates for Birmingham (Birm) and CHADS₂ Risk Scores by vWf level

•••

high plasma vWf level was defined as the top tertile (>158 IU/dL) of vWf levels in the study cohort. Low plasma vWf levels were defined as <158 IU/dL

				Full	cohort		
Derivation cohort							
ABC-stroke (trop	onin I)			0.68	(0 45 0 7	1)	
ABC-stroke (trop				0.60	(0.65, 0.7		
CHA DS VASA	bonin T)			0.67	(0.65, 0.7	5)	
CI 1A2032-4A3C				0.02	(0.00, 0.0.		
Validation cohort							
ABC-stroke (trop	oonin T)			0.66	(0.58, 0.7	4)	
CHA2DS2-VASc				0.58	(0.49, 0.6	7)	
Points	0 1	2	3 4	5	6 7	8	9 10
Prior stroke/TIA	No			Stroke/	ПА		
Age	44 55 6	5 75	90				
Troponin I (ng/L)	1 2	5 10	30	75 18	80		
NT-proBNP (ng/L)	25 50	100	200	400	800 15	00 300	0 590
Total Points	, , , , , , , , , , , , , , , , , , ,	5	10	 15	20	25	 30
1-year risk of stroke/SE			0.01	0.02 0.	03 0.05	0.1	0.15
3-year risk of stroke/SE		· · · · ·	1 1	0.05			_

ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in AF

Hijazi et al Eur Heart J 2016 doi:10.1093/eurheartj/ehw054

- ABC score derived from a cohort on anticoagulant treatment (ARISTOTLE trial) and validated in a mixed population cohort—some treated with anticoagulation and some not (49%).
- Laboratories and commercial assays have variance and differences in reproducibility or lower limits of detection.

Biomarkers (whether blood, urine, or imaging-based) will always improve on risk prediction scores based on clinical factors ... *at least statistically* [Note c-indexes all <0.70]

Long-Term Stroke Risk Prediction in Patients with AF: Comparison of ABC-Stroke & CHA₂DS₂-VASc Scores

Rivera-Caravaca Lip, Marin. J Am Heart Assoc. 2017;6:e006490. DOI: 10.1161/JAHA.117.006490

	C-Index	95% CI	P Value	z Statistic*	P Value*	IDI	P Value	NRI	P Value
At 3.5 y									
ABC-stroke score	0.663	0.634 to 0.690	<0.001	1.998	0.046	0.019	0.002	0.002	0.903
CHA ₂ DS ₂ -VASc score	0.600	0.567 to 0.625	< 0.001	7					
At 6.5 years									
ABC-stroke score	0.662	0.633 to 0.690	<0.001	1.574	0.116	0.019	0.002	-0.053	<0.001
CHA ₂ DS ₂ -VASc score	0.620	0.590 to 0.648	<0.001						

ABC-stroke indicates age, biomarkers (N-terminal fragment B-type natriuretic peptide, high-sensitivity troponin), and clinical history (prior stroke/transient ischemic attack); CHA2DS2-VASc, cardiac failure or dysfunction, hypertension, age \geq 75 (doubled), diabetes mellitus, stroke (doubled)—vascular disease, age 65 to 74 years and sex category (female); IDI, integrated discriminatory improvement; NRI, net reclassification index; ROC, receiver operating characteristic. *For C-index comparison.

- At 6.5 years, 6.64% patients categorized as low-medium risk with ABC-stroke score experienced an ischemic stroke, vs 1.59% low-medium risk with CHA₂DS₂-VASc score.
- Patients at low-medium risk with ABC-stroke had a median CHA₂DS₂-VASc score of 3 (IQR 2–4) and a high risk of stroke per every CHA₂DS₂-VASc score point (hazard ratio, 1.3; 95% CI, 1.09-1.70, p=0.007)

ABC-stroke score did not provide better long term predictive accuracy for stroke in 'real world' AF patients. CHA₂DS₂-VASc score performed well in identifying patients at "low risk," better than ABC-stroke

Refining Stroke and Bleeding Prediction in Atrial Fibrillation by Adding Consecutive Biomarkers to Clinical Risk Scores

Rivera-Caravaca .. Lip, Roldan. Stroke 2019;50(6):1372-1379.

Adding consecutive biomarkers, the predictive ability of CHA₂DS₂-VASc for ischemic stroke was not increased, whereas the predictive ability of HAS-BLED for major bleeding was only slightly enhanced statistically.



The net benefit and clinical usefulness of the biomarker-based models were marginal in comparison to the original scores based on clinical risk factors.

	C Index	95% Cl	Z Score*	P Value*	IDI, %	95% CI	P Value	NRI, %	95% CI	P Value
Ischemic stroke										
CHA2DS2-VASc	0.621	0.589-0.652								
+1 biomarker	0.634	0.602-0.655	0.721	0.471	1.70	0.00/4.40	0.060	-2.80	-13.20/19.00	0.667
+2 biomarkers	0.638	0.606-0.669	0.915	0.360	2.30	0.10/5.30	0.020	-5.60	-16.10/13.70	0.587
+3 biomarkers	0.641	0.610-0.672	1.153	0.249	2.70	0.70/5.30	<0.001	-4.50	-16.60/16.10	0.766
+4 biomarkers	0.639	0.607-0.670	1.024	0.306	2.70	0.60/5.50	0.020	-4.50	-14.10/15.30	0.826
+5 biomarkers	0.639	0.608-0.670	1.012	0.312	2.60	0.01/6.20	0.040	-3.30	-17.40/17.60	0.766
+6 biomarkers	0.639	0.608-0.670	1.022	0.307	2.60	0.30/6.20	0.020	-0.70	-10.90/16.70	0.999
Major bleeding										
HAS-BLED	0.600	0.561-0.625								
+1 biomarkers	0.636	0.605-0.667	2.158	0.031	4.00	0.90/7.80	<0.001	22.60	3.80/32.60	<0.001
+2 biomarkers	0.639	0.607-0.669	2.275	0.023	4.90	1.00/8.80	0.030	20.10	0.20/32.90	0.040
+3 biomarkers	0.639	0.607-0.669	2.249	0.025	5.20	1.90/8.90	<0.001	19.20	1.40/32.50	0.020
+4 biomarkers	0.638	0.606-0.669	2.188	0.029	5.00	1.60/8.70	<0.001	19.40	3.00/33.70	0.020
+5 biomarkers	0.635	0.604-0.666	2.003	0.045	5.00	1.90/8.80	<0.001	19.60	4.80/32.70	<0.001
+6 biomarkers	0.635	0.604-0.666	2.023	0.043	5.30	1.90/9.20	0.020	20.30	0.40/34.20	0.020

Predicting Adverse Events beyond Stroke and Bleeding with the ABC-Stroke and ABC-Bleeding Scores in Patients with AF: The Murcia AF Project

Camelo-Castillo .. Lip et al Thromb Haemost 2020;120(8):1200-1207.

	ABC-stroke	ABC-bleeding	<i>p</i> -Value ^a
	c-index (95% Cl)	c-index (95% CI)	
Myocardial	0.535	0.542	0.880
infarction	(0.504–0.566)	(0.511–0.572)	
Acute heart	0.600	0.614	0.504
failure	(0.564–0.624)	(0.584–0.644)	
Composite cardiovascular events	0.644 (0.615–0.674)	0.644 (0.613–0.672)	0.946
All-cause	0.704	0.726	0.187
mortality	(0.676–0.732)	(0.698–0.753)	

^ap-Value for c-index comparison.

Decision curve analyses for the primary endpoints.

 The ABC-stroke and ABC-bleeding scores demonstrated similar predictive ability for outcomes beyond stroke and bleeding, including MI, acute HF, a composite of cardiovascular events, and all-cause deaths.
Consistent with nonspecificity of biomarkers that predict "sick" patients or poor prognosis overall. European Heart Journal Advance Access published December 20, 2012



European Heart Journal doi:10.1093/eurheartj/ehs435 REVIEW

Controversies in cardiovascular medicine

Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why?

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'..... the value of clinical risk scores would be enhanced by biomarkers that can include blood markers (e.g. vWf), urine (for example, proteinuria, eGFR or creatinine clearance), cardiac imaging (echocardiography, whether transthoracic or transoesophageal) and/or cerebral imaging (e.g. CT or MRI imaging) which can offer incremental predictive value for the identification of 'high risk' subjects.

..... this would be at the cost of reduced simplicity and practicality, limiting its (immediate) 'quick' use in everyday clinical practice'

Beyond CHA₂DS₂VASc there remains a high residual risk

Cause of Death and Predictors of All-Cause Mortality in Anticoagulated Patients With Nonvalvular AF: Data From ROCKET AF

Pokorney et al J Am Heart Assoc. 2016;5: e002197 doi: 10.1161/JAHA.115.002197

	Rivaroxaban (n=582)	Warfarin (n=632)	HR (95% CI)	P Value
All-cause mortality	582 (4.5)	632 (4.9)	0.92 (0.82-1.03)	0.15
Vascular death	375 (2.9)	401 (3.1)	0.94 (0.81-1.08)	0.35
Nonvascular death	148 (1.2)	157 (1.2)	0.94 (0.75-1.18)	0.61
Death unknown cause	59 (0.5)	74 (0.6)	0.80 (0.57-1.12)	0.20
Sudden/unwitnessed death	169 (1.3)	174 (1.4)	0.97 (0.79-1.20)	0.79
CHF/shock cause of death	88 (0.7)	69 (0.5)	1.28 (0.93-1.75)	0.13
Malignancy cause of death	63 (0.5)	55 (0.4)	1.14 (0.80-1.64)	0.46
Intracranial hemorrhage death	27 (0.2)	43 (0.3)	0.63 (0.39-1.02)	0.06

Data are summarized as number of events (event rate per 100 patient-years of follow-up), unless otherwise indicated. CHF indicates congestive heart failure; HR, hazard ratio.

AF patients anticoagulated for nonvalvular atrial fibrillation, ~7 in 10 deaths were cardiovascular, whereas <1 in 10 deaths were caused by nonhemorrhagic stroke or systemic embolism. Optimal prevention and treatment of heart failure, renal impairment, chronic obstructive pulmonary disease, and diabetes may improve survival.

We make it complicated

Stroke Risk Factors Beyond the CHA₂DS₂-VASc Score: Can We Improve Our Identification of "High Stroke Risk" Patients With Atrial Fibrillation?

Szymanski .. Lip et al Am J Cardiol 2015 http://dx.doi.org/10.1016/j.amjcard.2015.0 8.049

Proposed flow chart for thromboembolic risk assessment in atrial fibrillation patients



Impact of clinical phenotypes on management and outcomes in European AF patients: the ESC-EHRA EORP-AF General Long- Term Registry

Proietti ...Lip. BMC Medicine 2021 19:256 https://doi.org/10.1186/s12916-021-02120-3





	Univariate		Multivariable ^a	
	HR (95% CI)	Р	HR (95% CI)	Р
Cardiovascular E	vents, <i>n</i> (%)			
Cluster 1	1.85 [1.46–2.34]	< .001	1.88 [1.48–2.38]	< .001
Cluster 2 (Ref.)	_	-	_	-
Cluster 3	2.82 [2.24–3.55]	< .001	2.87 [2.27–3.62]	< .001
All-cause death,	n (%)			
Cluster 1	2.55 [2.03–3.21]	< .001	2.50 [1.98–3.15]	< .001
Cluster 2 (Ref.)	_	-	_	_
Cluster 3	3.55 [2.83–4.46]	< .001	3.42 [2.72–4.31]	< .001
Composite outco	ome, <i>n</i> (%)			
Cluster 1	2.09 [1.74–2.51]	< .001	2.09 [1.74–2.51]	< .001
Cluster 2 (Ref.)	_	-	_	_
Cluster 3	2.81 [2.34–3.37]	< .001	2.79 [2.32–3.35]	< .001

Legend: ^aadjusted for type of AF, EHRA score, use of OAC. *HR* hazard ratio. For other acronyms, please see previous tables' legends

Improving dynamic stroke risk prediction in non-anticoagulated patients with and without AF: comparing common clinical risk scores and ML algorithms

Lip et al EHJ-QCCO 2021: doi:10.1093/ehjqcco/qcab037



Figure I External validation for three sets of three clinical rule-based models: (A) Set 1: multi-morbid index 'MMC1' (C index 0.8451, 95% CI 0.8427–0.8476), CHADS₂ (C index 0.7488, 95% CI 0.746–0.7516), CHA₂DS₂VASc (C index 0.7801, 95% CI 0.7772–0.7831); (B) Set 2: multi-morbid index/AF status (C index 0.8508, 95% CI 0.8483–0.8532), CHADS₂/AF status (C index 0.7694, 95% CI 0.7667–0.7722), CHA₂DS₂VASc/AF status (C index 0.796, 95% CI 0.7931–0.7989); (C) Set 3: multi-morbid index/AF status/Medicare status (C index 0.8577, 95% CI 0.8343, 95% CI 0.8319–0.8368), CHA₂DS₂VASc/AF status/Medicare status (C index 0.8285, 95% CI 0.8319–0.8368), CHA₂DS₂VASc/AF status/Medicare status (C index 0.8285, 95% CI 0.8259–0.8312).



The best prediction model was derived on the basis of non-linear formulations using ML criteria, with the highest c-index was obtained for logistic regression [0.892; 95% CI 0.886– 0.898] with consistency on external validation (0.891; 95% CI 0.882–0.9).

These were significantly higher than those based on the conventional stroke risk scores (CHADS₂: 0.7488, 95% Cl 0.746-0.7516;

CHA₂DS₂-VASc: 0.7801, 95% CI 0.7772–0.7831) and multi-morbid index (0.8508, 95% CI 0.8483–0.8532).

Or we can keep it simple and practical

'A' Avoid stroke/anticoagulation

The default is stroke prevention* unless 'low risk'

... given the limitations of (all) risk scores

*Stroke prevention means oral anticoagulation, whether as well managed warfarin with good TTR (>70%) or (ideally) NOAC





ESC GUIDELINES

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)



2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary*

Thinking outside the CHA₂DS₂VASc Box Let me conclude with this:

Impact of adherence to the ABC pathway on clinical outcomes in patients with AF

Romiti .. Lip, Proietti. Thromb Haemostat 2022 Mar;122(3):406-414

