

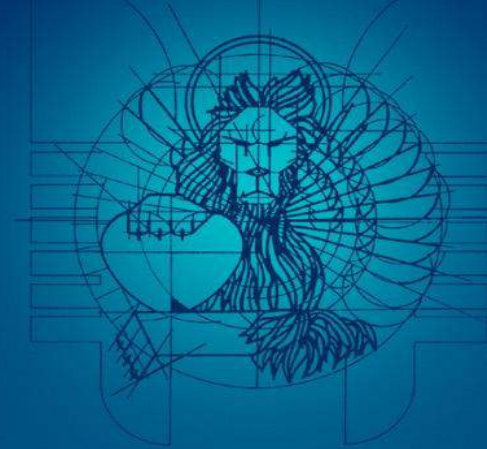
XV World Congress of Arrhythmias, Beijing, China - 17-20 September, 2015

Evaluate Risk of Stroke & Bleeding in AF Patients

Antonio Raviele, MD, FESC, FHRS

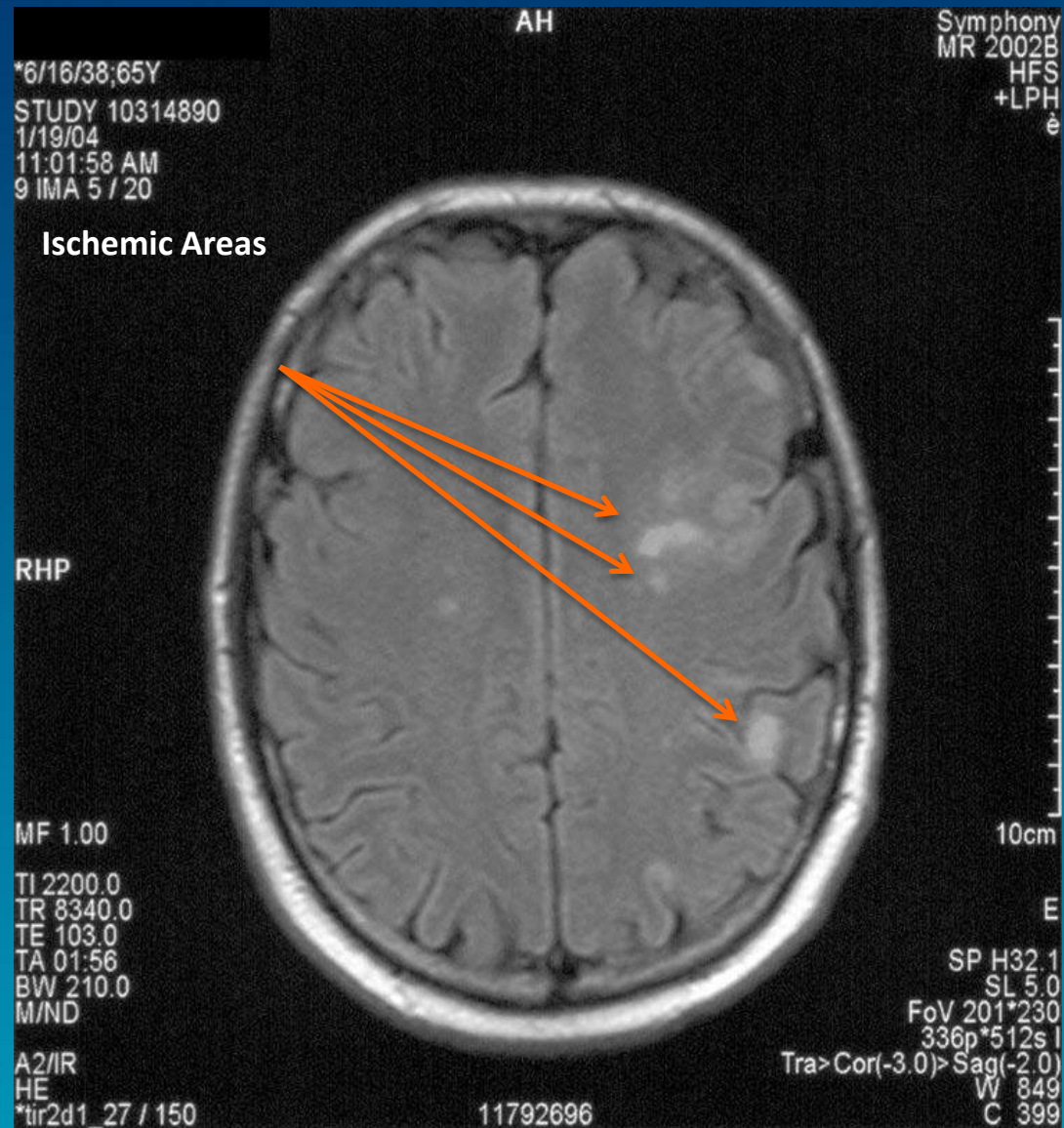
President ALFA – Alliance to Fight Atrial fibrillation - Venice, Italy

Main Issues

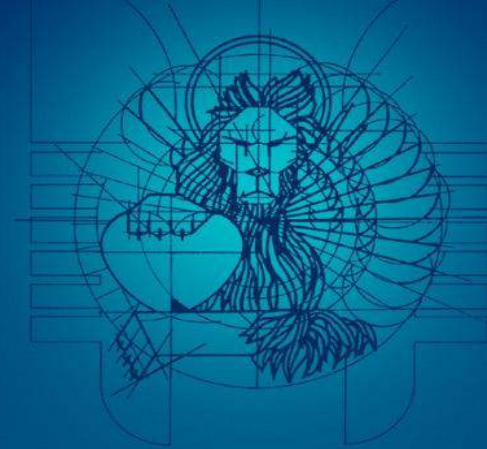


- ✓ Reasons for the evaluation
- ✓ Stroke risk stratification
- ✓ Bleeding risk stratification
- ✓ Net clinical benefit of OACs
- ✓ Indications to antithrombotic treatment

Cerebral embolism as complication of AF



AF & Stroke



Annual Incidence in pts with AF

AF	————→	4,5%
Controls	————→	0,2% - 1,4%

(The SPAF Investigators. AIM 1992; 116: 1 – 5)

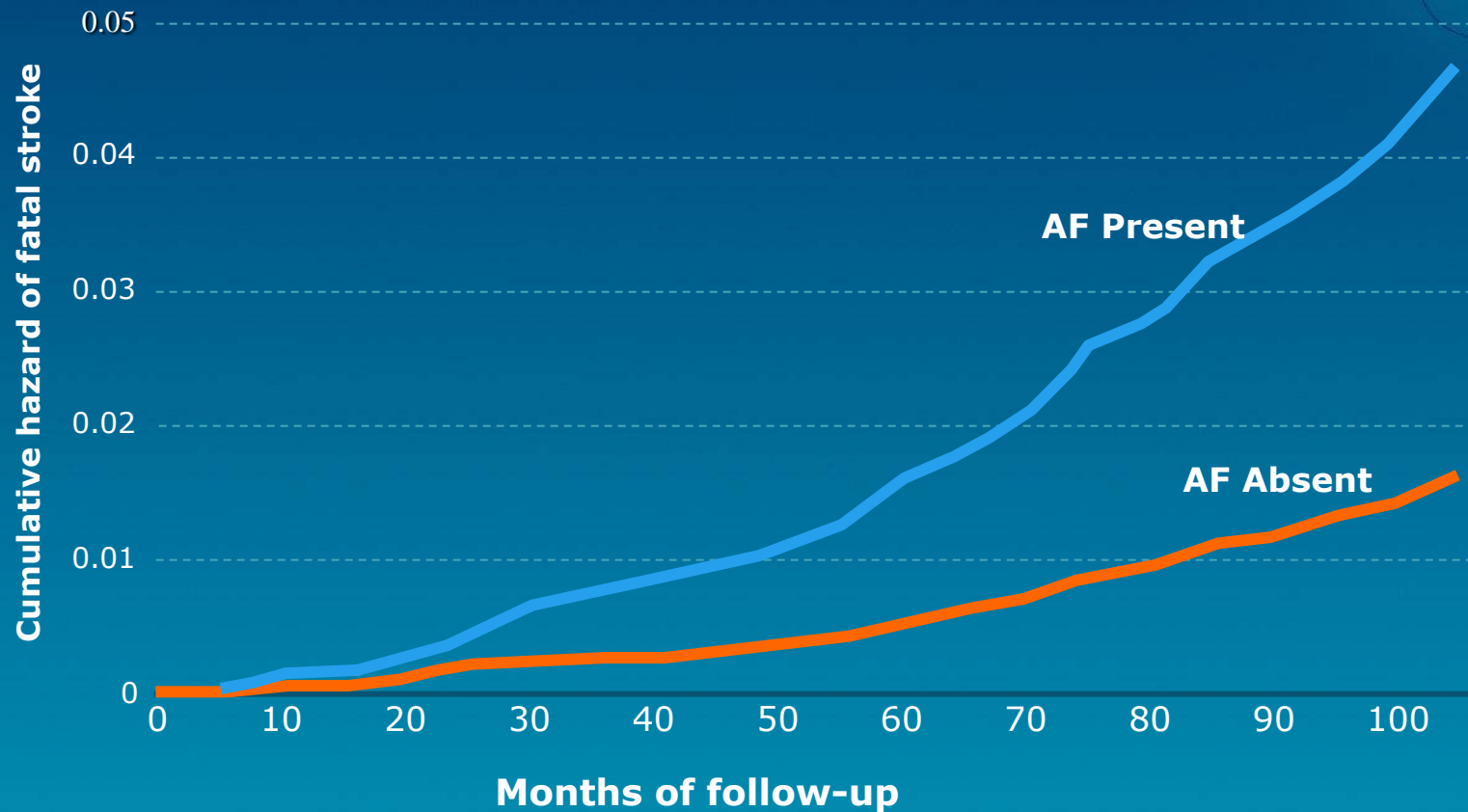
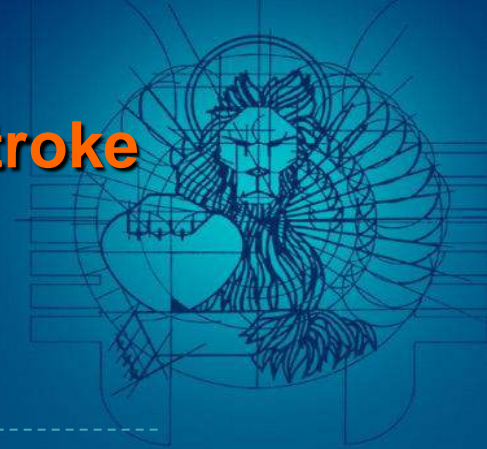
Strokes in patients with Afib are more severe

The European Community Stroke Project

- Multi-centre, multi-national hospital-based registry involving 4462 patients hospitalized for first stroke
- AFib diagnosed in 803 stroke patients (18%)
- At 3 months, 32.8% of stroke patients with AFib were dead vs 19.9% of stroke patients without AFib
- AFib increased by approximately 50% the probability of remaining disabled

AFib is Associated with Progressive Risk of Stroke

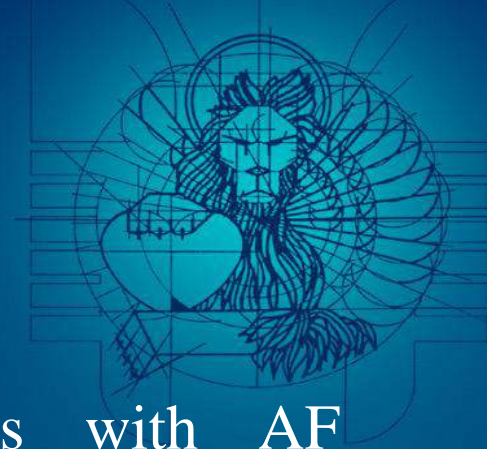
- Independent predictor of stroke recurrence and severity



Use of Antithrombotic Agents for Stroke Prevention in Patients with Atrial Fibrillation

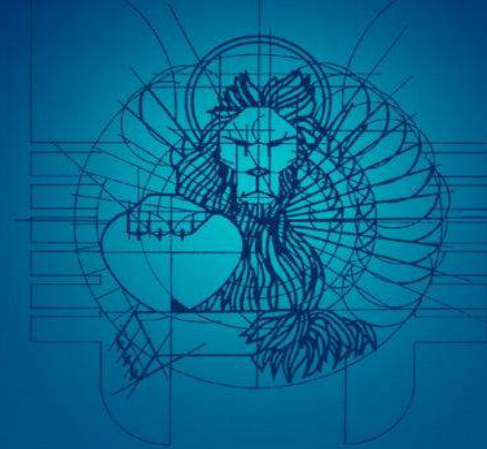
Antithrombotic Agents	Stroke/SE Risk Reduction (%)	Annualized Major Bleeding Rate (%)	Annualized Severe Bleeding Rate (%)	Annualized ICH Rate (%)
Vitamin K Antagonists	64% vs no treatment	3.40-6.0%	1.36-2.18%	0,74-0.85%
No VKA Oral Anticoagulants	+19% vs VKA	1.60-4.10%	0.44-1.45%	0.23-0.50%
Dabigatran 110-150 mg	+9% +34% vs VKA	2.70-3.10%	1.22-1.45%	0.23-0.30%
Rivaroxaban	+21% vs VKA	3.60%	1.0%	0.50%
Apixaban	+21% vs VKA	4.10%	1.29%	0.33%
Edoxaban 30-60 mg	-7% +21% vs VKA	1.60-2.70%	0.44-0.70%	0.26-0.39%
Aspirin	19% vs no treatment	1.20-1.30%	1.0%	0.20-0.40%
Aspirin + Clopidogrel	+28% vs Aspirin	2.0-2.41%	1.50-1.70%	0.40%

Reasons for Risk Stratification



- The risk of stroke and bleeding in patients with AF is not homogeneous and may vary considerably from subject to subject according to the presence or not of several clinical and laboratory factors.
- Consequently, it is necessary in clinical practice to adequately assess the risk of both stroke and bleeding in the single subject before starting OAC therapy in order to avoid treatment when it is harmful (that is when the risks of OAC therapy outweigh the potential benefits).

Main Issues



- ✓ Reasons for the evaluation
- ✓ Stroke risk stratification
- ✓ Bleeding risk stratification
- ✓ Net clinical benefit of OACs
- ✓ Indications to antithrombotic treatment

Table 1. Risk Factors Included in Various Clinical Stroke Risk Stratification Schema and Guidelines

	Risk Factors							Other Factors
	Age, y	Female Sex	Prior TE Event	Hypertension	Heart Failure	Diabetes Mellitus	Vascular Disease	
Scheme								
SPAF, ²⁰ 1999	>75 ^a	✓ ^a	✓	✓		✓		
AFI, ²¹ 1994	65-75 >75		✓	✓		✓		
CHADS ₂ , ²² 2001	≥75		✓	✓	✓	✓		
Framingham, ²³ 2003	✓	✓	✓	✓		✓		
van Walraven, ²⁴ 2003			✓	✓		✓	✓	
Rietbrock, ²⁵ 2008	✓	✓	✓			✓		
CHA ₂ DS ₂ -VASc, ²⁶ 2009	65-74 ≥75	✓	✓	✓	✓	✓	✓	
QStroke, ²⁷ 2013	✓	✓	✓	✓	✓	✓	✓	Many others
ATRIA, ²⁸ 2013	✓	✓	✓	✓	✓	✓	✓	Proteinuria and eGFR; different weighting for primary and secondary prevention
Guidelines								
ACCP, ²⁹ 2012	65-74 >75	✓	✓	✓	✓	✓	✓	CHADS ₂ score, 0, non-CHADS ₂ risk factors (similar to CHA ₂ DS ₂ -VASc) should be considered
ESC, ⁴ 2012	65-74 ≥75	✓	✓	✓	✓	✓	✓	Based on CHA ₂ DS ₂ -VASc
CCS, ³⁰ 2014	≥65		✓	✓	✓	✓		
AHA/ACC/HRS, ⁵ 2014	65-74 ≥75	✓	✓	✓	✓	✓	✓	Based on CHA ₂ DS ₂ -VASc
NICE, ⁴ 2014	65-74 ≥75	✓	✓	✓	✓	✓	✓	Based on CHA ₂ DS ₂ -VASc

Abbreviations: ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; AHA/ACC/HRS, American Heart Association, American College of Cardiology, and Heart Rhythm Society; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; SPAF, Stroke Prevention in Atrial Fibrillation; TE, thromboembolism. CHADS₂: C, congestive heart failure, H, hypertension, A, age 65 through 74 years,

D, diabetes, and S₂, previous stroke, transient ischemic attack (TIA), or systemic embolism; CHA₂DS₂-VASc: C, congestive heart failure, H, hypertension, A₂, age at least 75 years, D, diabetes, S₂, previous stroke, TIA, or systemic embolism, V, vascular disease, Sc, sex category female sex.

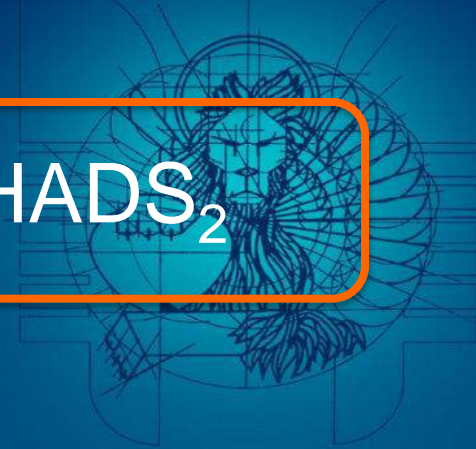
^a Age and female sex combined are a single risk factor.

CHADS₂ score system



	Risk factor	Points	CHADS ₂ score	Patients (n=1733)	Annualized stroke rate (%/year)
C	Congestive HF (recent)	1	0	120	1,9
H	Hipertension (history of)	1	1	463	2,8
			2	523	4,0
A	Age ≥75 years	1	3	337	5,9
D	Diabetes mellitus	1	4	220	8,5
			5	65	12,5
S ₂	Stroke/TIA	2	6	5	18,2

Stroke risk stratification according to CHADS₂



Risk Category	Predicted Risk
CHADS ₂ = 0	low
CHADS ₂ = 1	moderate
CHADS ₂ ≥ 2	high

Limitations of CHADS₂ score



- ✓ CHADS₂ score system has only **modest predictive value** (c-statistic 0.58 – 0.67)
- ✓ It works quite well in identifying pts at **high risk of stroke** but is inadequate in stratifying those at moderate - low risk
- ✓ Several cohorts have shown that **up to 30-50%** of patients are classified by CHADS₂ as **intermediate risk**, thus falling in the grey zone where recommendation for OAC therapy is not always clear
- ✓ Patients categorized as **low risk** by CHADS₂ score, and thus not necessitating OAC according to guidelines, may have an annual stroke rate as high as **3.2%**

Table 1. Risk Factors Included in Various Clinical Stroke Risk Stratification Schema and Guidelines

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van Walraven, ²⁴ 2003			✓	✓		✓	✓	
Rietbrock, ²⁵ 2008	✓	✓	✓			✓		
CHA ₂ DS ₂ -VASc, ²⁶ 2009	65-74 ≥75	✓	✓	✓	✓	✓	✓	
QStroke, ²⁷ 2013	✓	✓	✓	✓	✓	✓	✓	Many others
ATRIA, ²⁸ 2013	✓	✓	✓	✓	✓	✓	✓	Proteinuria and eGFR; different weighting for primary and secondary prevention
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ACCP, ²⁹ 2012	65-74 >75	✓	✓	✓	✓	✓	✓	CHADS ₂ score, 0, non-CHADS ₂ risk factors (similar to CHA ₂ DS ₂ -VASc) should be considered Based on CHA ₂ DS ₂ -VASc Based on CHA ₂ DS ₂ -VASc Based on CHA ₂ DS ₂ -VASc
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CCS, ³⁰ 2014	≥65		✓	✓	✓	✓		
AHA/ACC/HRS, ⁵ 2014	65-74 ≥75	✓	✓	✓	✓	✓	✓	
NICE, ⁴ 2014	65-74 ≥75	✓	✓	✓	✓	✓	✓	Based on CHA ₂ DS ₂ -VASc

Abbreviations: ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; AHA/ACC/HRS, American Heart Association, American College of Cardiology, and Heart Rhythm Society; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; SPAF, Stroke Prevention in Atrial Fibrillation; TE, thromboembolism. CHADS₂: C, congestive heart failure, H, hypertension, A, age 65 through 74 years,

D, diabetes, and S₂, previous stroke, transient ischemic attack (TIA), or systemic embolism; CHA₂DS₂-VASc: C, congestive heart failure, H, hypertension, A₂, age at least 75 years, D, diabetes, S₂, previous stroke, TIA, or systemic embolism, V, vascular disease, Sc, sex category female sex.

^a Age and female sex combined are a single risk factor.

CHA₂DS₂-VASc score system



	Risk Factor	Points	CHA ₂ DS ₂ -VASc score	Patients (n=7329)	Annualized stroke rate (%/year)*	Annualized stroke rate (%/year)**
C	Congestive HF(EF<40%)	1	0	1	0	0.78
H	Hypertension	1	1	422	1,3	2.01
A ₂	Age ≥75 years	2	2	1230	2,2	3.71
D	Diabetes mellitus	1	3	1730	3,2	5.92
S ₂	Stroke/TIA/TE	2	4	1718	4,0	9.27
V	Vascular disease*	1	5	1159	6,7	15.26
A	Age 65-74 years	1	6	679	9,8	19.78
Sc	Sex category (female sex)	1	7	294	9,6	21.50
*prior MI, peripheral artery disease, or aortic plaque			8	82	6,7	22.38
			9	14	15,2	23.64

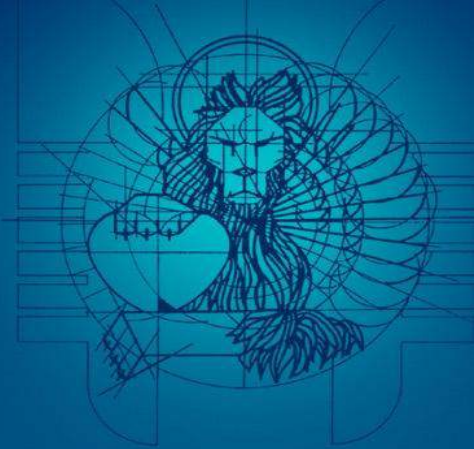
*Lip *et al.* Stroke 2010; 41: 2731-2738; **Olesen JB *et al.* 2011; 342: d124

Stroke risk stratification according to CHA₂DS₂-VASc

Risk Category	Predicted Risk
CHA ₂ DS ₂ -VASc = 0	low
CHA ₂ DS ₂ -VASc = 1	moderate
CHA ₂ DS ₂ -VASc ≥ 2	high

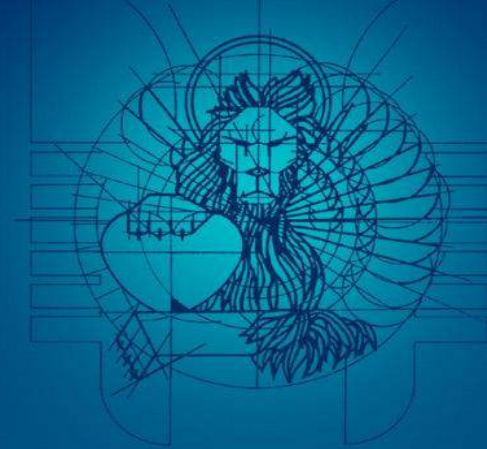
Importantly, female sex is considered a risk factor only in patients older than 65 years and when at least another additional risk factor is present.

Advantages of CHA₂DS₂-VASc score



- ✓ It is best at identifying “truly low-risk” patients for whom the absolute risks of stroke/TIA or systemic embolism are less than 1% per year
- ✓ It is as good as-possibly better than-the CHADS₂ for predicting high-risk patients (about three-fourths)
- ✓ It classifies only 15% of patients as intermediate risk, a category for which OAC is still somewhat controversial

Bleeding Score Systems



- ✓ **HAS-BLED**
- ✓ **HEMORR₂AGES**
- ✓ **ATRIA**
- ✓ **Outpatient bleeding score**
- ✓ **Kuijer bleeding score**
- ✓ **Shireman bleeding score**
- ✓ **RIETE**

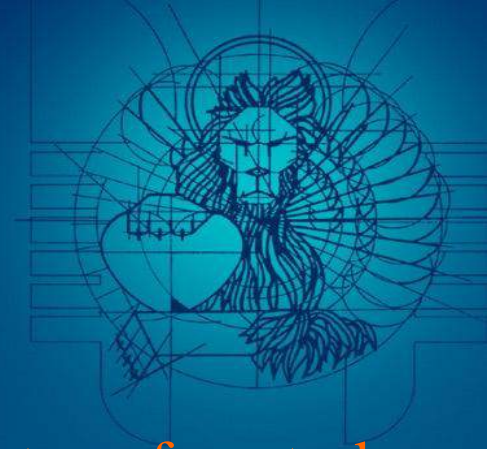
HAS-BLED score system

	Risk factor	Points	HAS-BLED score	Annualized bleeding rate (%/year)
H	Hypertension (SBP >160 mm Hg)	1	0	1.13
A	Abnormal renal and liver function	1 o 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding tendency/predisposition	1	3	3.74
L	Labile INRs (TTR <60%)	1	4	8.70
E	Elderly (age >65 y, frail condition)	1	5	12.50
D	Drugs or alcohol excess	1 o 2	6	16.48 for ≥6 points
			7	
			8	
			9	

Bleeding risk stratification according to HAS-BLED

Risk Category	Predicted Risk
HAS-BLED = 0	low
HAS-BLED = 1-2	moderate
HAS-BLED = ≥ 3	high

Considerations (1)

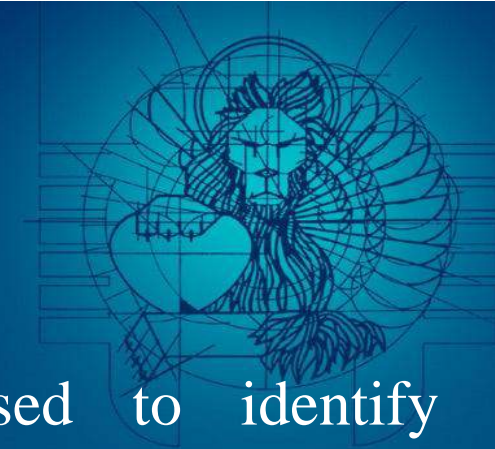


- ✓ Many risk factors for bleeding are also risk factors for stroke.

Thus it is not rare that patients at high risk of stroke are also at high risk of bleeding.

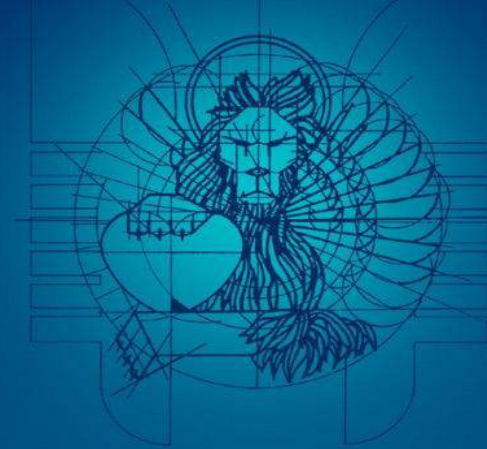
- ✓ A high HAS-BLED score (≥ 3) should not be a contraindication or a reason to discontinue treatment with OACs, as the reduction in stroke risk on anticoagulation usually far exceeds the small elevation in serious bleeding risk.

Considerations (2)



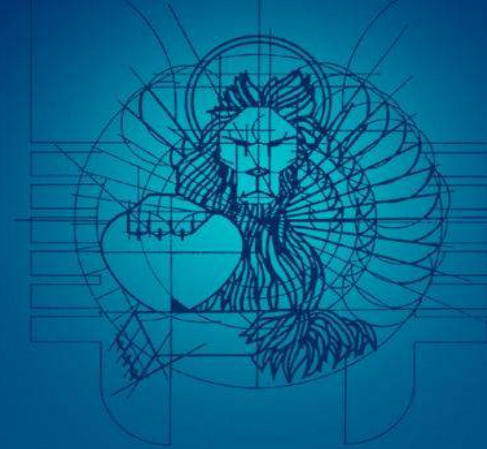
- ✓ A high HAS-BLED score (≥ 3) can be used to identify potentially correctable risk factors that contribute to bleeding such as uncontrolled hypertension, INR lability, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs, and excessive alcohol intake
- ✓ It should also alert physicians to schedule more regular follow-up visits and provide straightforward warning about the necessity of avoiding falls and not engaging in high –risk activities

Main Issues



- ✓ Reasons for the evaluation
- ✓ Stroke risk stratification
- ✓ Bleeding risk stratification
- ✓ Net clinical benefit of OACs
- ✓ Indications to antithrombotic treatment

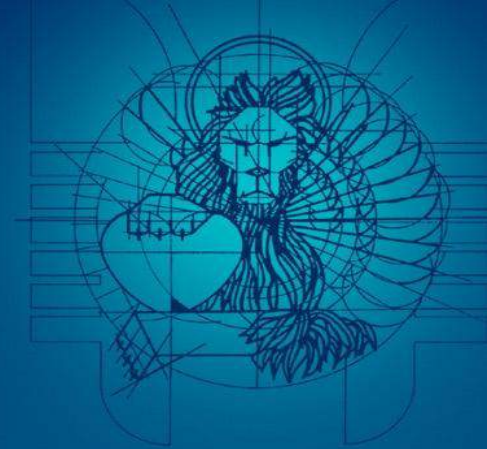
Critical question



Should this patient be treated with OACs



OAC / Net Clinical Benefit

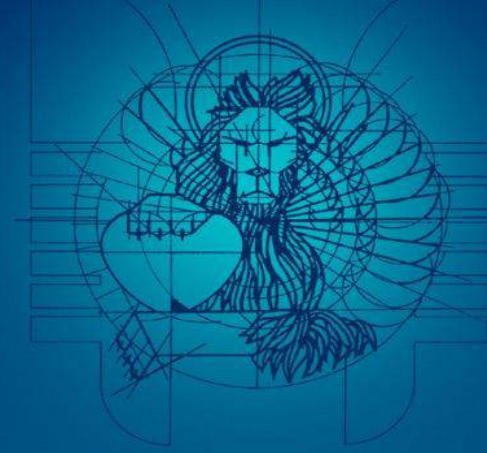


Potential benefit
of ischemic
stroke prevention



Potential risk
of serious bleeding,
in particular ICH

OAC / Net Clinical Benefit



$$(IS_{\text{off OAC}} - IS_{\text{on OAC}}) - 1.5 \times (ICH_{\text{on OAC}} - ICH_{\text{on OAC}})$$

number of IS avoided by OACs - number of ICH attributable to OACs x 1.5

to account for the generally more disastrous effects of an intracranial bleed
compared with an ischemic stroke

Net Clinical Benefit of Warfarin in Patients With Atrial Fibrillation

A Report From the Swedish Atrial Fibrillation Cohort Study

Leif Friberg, MD, PhD; Mårten Rosenqvist, MD, PhD; Gregory Y.H. Lip, MD

Circulation 2012; 125: 2298-2307

Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study

Jonas Bjerring Olesen^{1,2}; Gregory Y. H. Lip²; Jesper Lindhardsen¹; Deirdre A. Lane²; Ole Ahlehoff¹; Morten Lock Hansen¹; Jakob Raunsø¹; Janne Schurmann Tolstrup³; Peter Riis Hansen¹; Gunnar Hilmar Gislason¹; Christian Torp-Pedersen¹

Thromb Haemost 2011; 106: 739-749

Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

Amitava Banerjee¹; Deirdre A. Lane¹; Christian Torp-Pedersen²; Gregory Y. H. Lip¹

Thromb Haemost 2012; 107: 584-589

Net Clinical Benefit for Oral Anticoagulation, Aspirin, or No Therapy in Nonvalvular Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex).

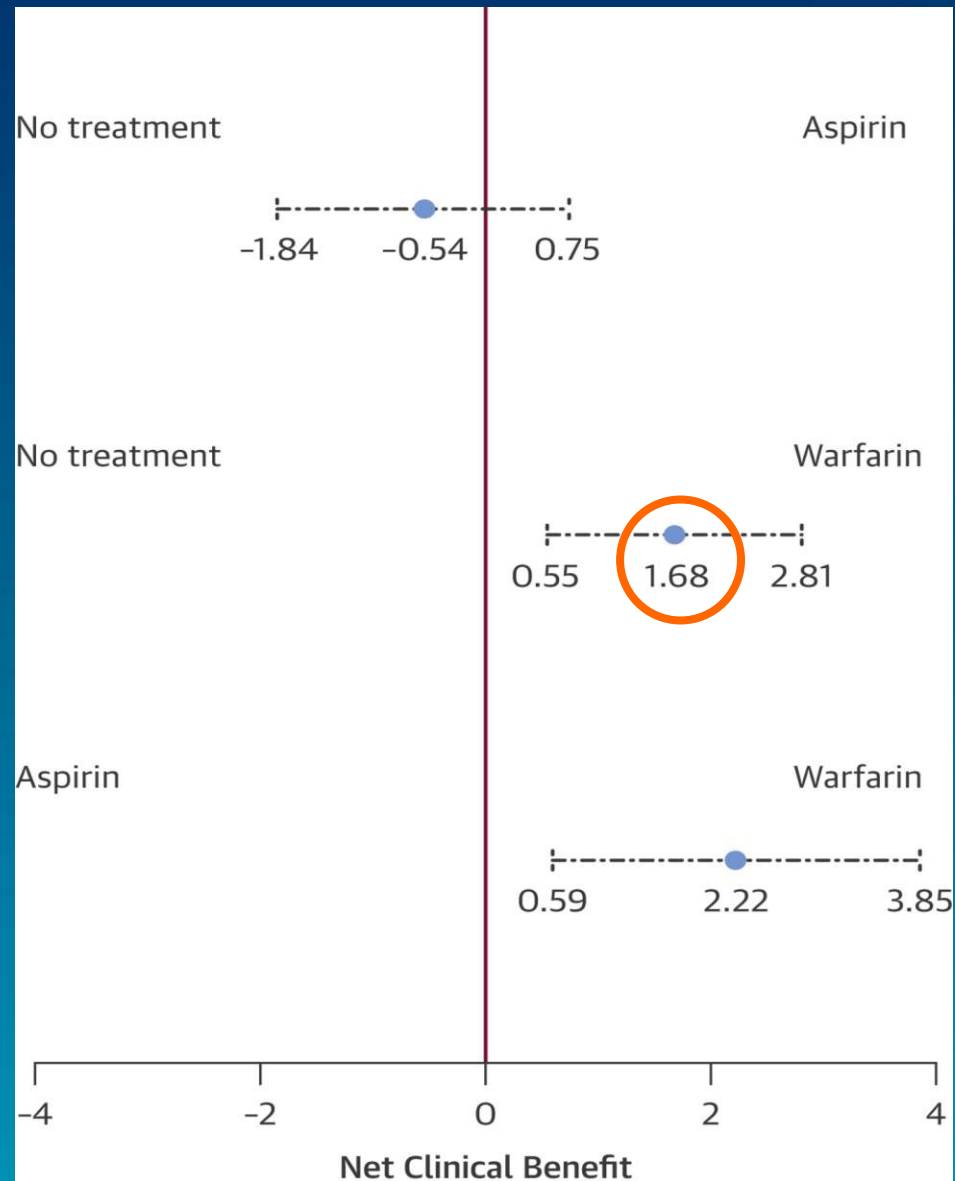
Lip GY, Skjøth F, Rasmussen LH, Nielsen PB, Larsen TB.

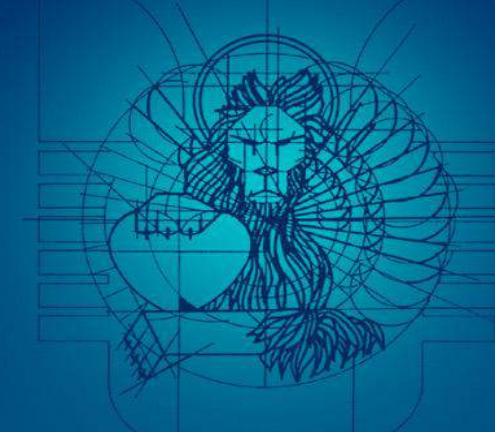
J Am Coll Cardiol. 2015 ; 66: 488-90.

Table 4: Net clinical benefit (95% confidence interval) of antithrombotic treatment

	Stroke				VKA	
	Ischaemic		Haemorrhagic		HAS-BLED score	
	N (%)	Person to years at risk	N (%)	Person to years at risk	Score ≤2	Score ≥3
CHA₂DS₂-VASc						
Score 0	46 (0.4)	66,020	32 (0.3)	66,076	-0.11 (-0.20 to -0.03)	-
Score 1	170 (0.9)	86,370	108 (0.6)	86,474	-0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)
Score 2-9	6,994 (6.2)	354,881	1,241 (1.1)	357,817	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)
Values >0 favours treatment. If less than 200 person-years in treatment in a cell the net clinical benefit is not calculated. CHA ₂ DS ₂ -VASc, and HAS-BLED: see text; VKA: vitamin K antagonist.						

Net Clinical Benefit for Oral Anticoagulation, Aspirin, or No Therapy in Nonvalvular Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA₂DS₂-VASc Score (Beyond Sex)



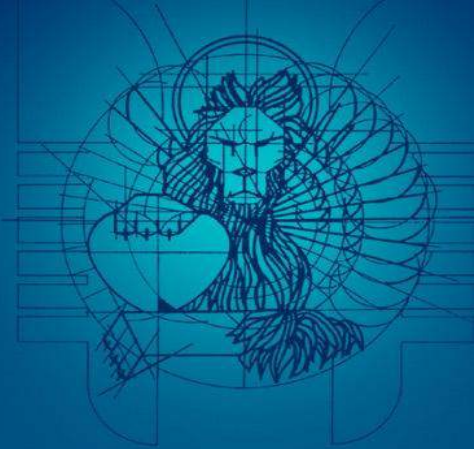


Net clinical benefit (95% confidence interval) of anticoagulant versus no treatment												
Warfarin		Dabigatran 110 mg		Dabigatran 150 mg		Rivaroxaban (ITT)		Rivaroxaban (OTA)		Apixaban		
HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	
CHA ₂ DS ₂ -VASc score												
0	-0.11 (-0.20,-0.03)	-	1.75 (1.40,2.15)	-	1.36 (1.07,1.68)	-	0.74 (0.53,0.96)	-	0.68 (0.49,0.89)	-	0.84 (0.62,1.08)	
1	-0.02 (-0.15,0.11)	0.25 (-0.86,1.36)	1.40 (1.11,1.68)	1.67 (0.40,2.93)	1.09 (0.84,1.33)	1.36 (0.13,2.58)	0.62 (0.42,0.82)	0.89 (-0.29,2.07)	0.58 (0.38,0.77)	0.85 (-0.33,2.02)	0.70 (0.49,0.96)	1.38 (0.14,2.60)
2-9	1.19 (1.07,1.32)	2.21 (1.93,2.50)	2.37 (2.20,2.54)	3.39 (3.06,3.72)	2.08 (1.92,2.24)	3.10 (2.78,3.42)	1.71 (1.57,1.86)	2.73 (2.43,3.04)	1.67 (1.53,1.81)	2.69 (2.39,2.99)	1.77 (1.62,1.92)	3.13 (2.81,3.45)

Net clinical benefit [events prevented per 100 person-years (95% confidence interval)] is calculated as annualised (thromboembolism rate off warfarin – thromboembolism rate on warfarin) – 1.5x (ICH rate on warfarin - ICH rate off warfarin), based on the study by Singer et al1. ITT: Intention-to-treat analysis; OTA: On treatment analysis.

P.S. Patients with a high HAS-BLED score seem to derive the highest net clinical benefit

Threshold for starting OAC therapy

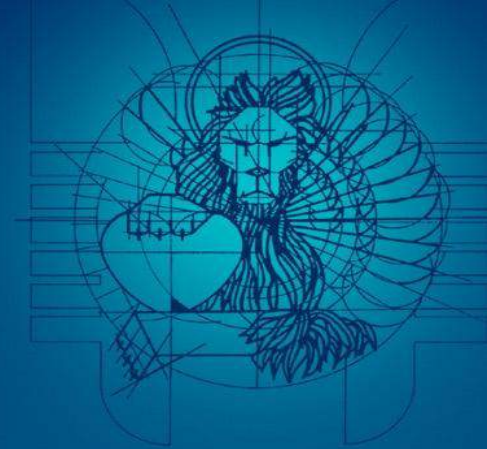


Stroke rate per year

- ✓ Warfarin: 1.7%
- ✓ NOACs: 0.9%

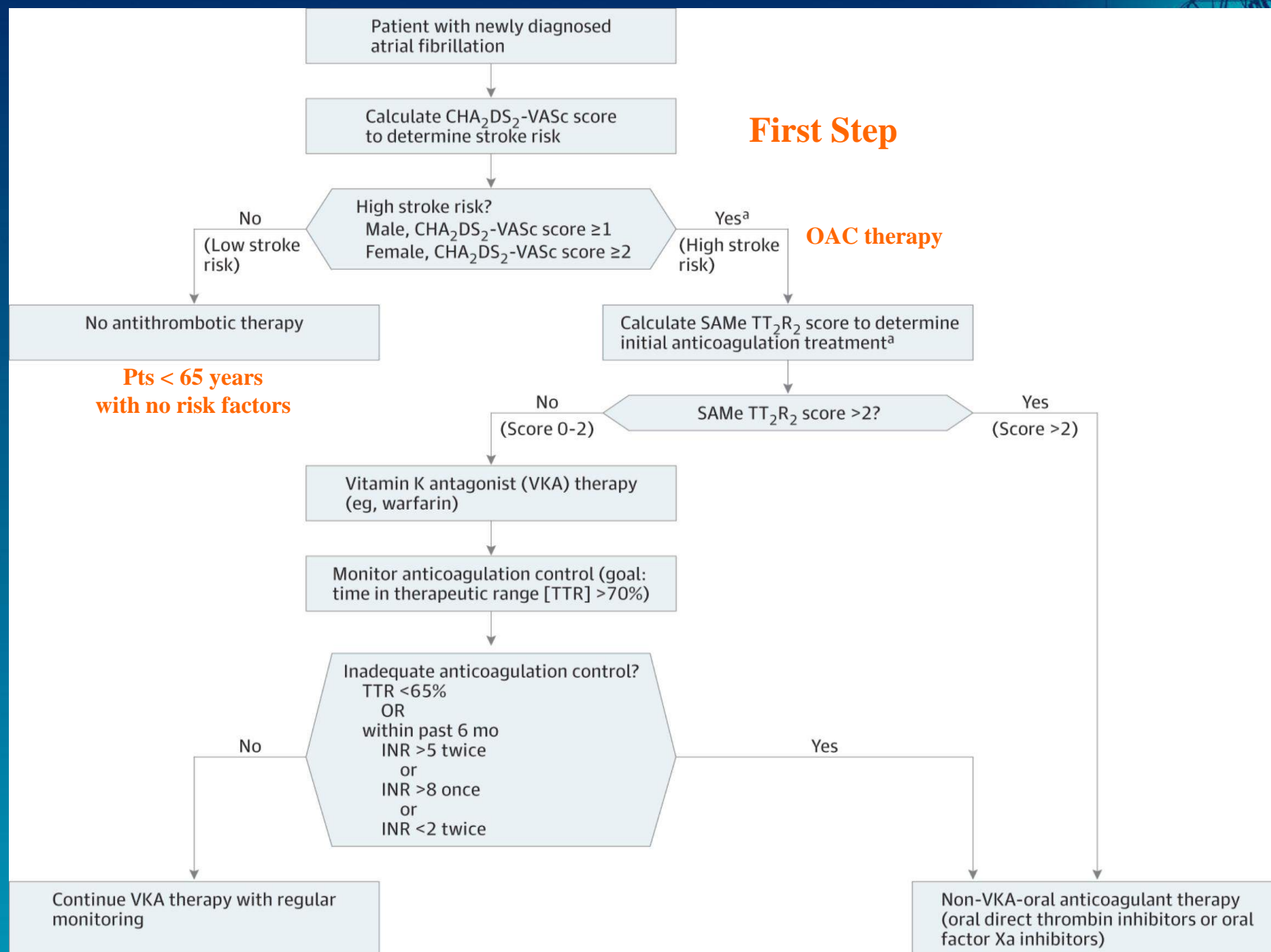
taking into account that NOACs reduce by 50% the annual incidence of ICH compared to warfarin

Main Issues



- ✓ Reasons for the evaluation
- ✓ Stroke risk stratification
- ✓ Bleeding risk stratification
- ✓ Net clinical benefit of OACs
- ✓ Indications to antithrombotic treatment

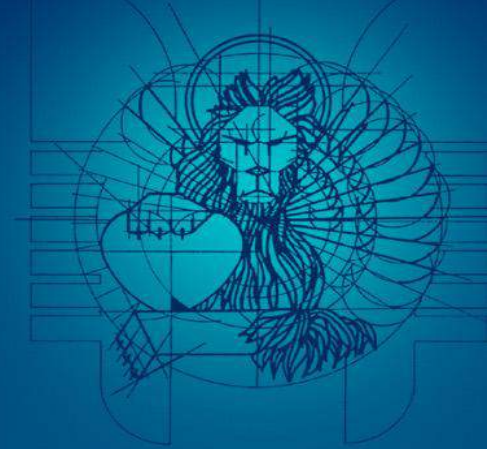
Algorithm for Risk Stratification and Selection of Anticoagulation Therapy for Stroke Prevention in AF



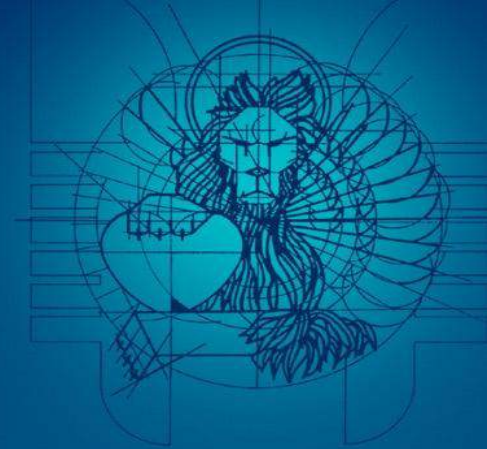
Conclusions (1)



- ✓ Decisions regarding appropriate stroke prevention require **individual assessment of stroke and bleeding risk** on anticoagulation with warfarin and NOACs
- ✓ Use of risk scores such as **CHA₂DS₂-VASc** and **HAS-BLED** can help in the selection of appropriate management strategies and antithrombotic agents
- ✓ A **CHA₂DS₂-VASc** of 1 in male and 2 in female is usually sufficient to **start OAC therapy**, as the reduction in stroke risk on anticoagulation usually far exceeds the small elevation in serious bleeding risk.



Main Issues



- ✓ Reasons for the evaluation
- ✓ Stroke risk stratification
- ✓ Bleeding risk stratification
- ✓ Net clinical benefit of OACs
- ✓ Indications for antithrombotic treatment
- ✓ Which OAC to start

Figure 1. Percent of patients free from stroke over time, stratified by time spent in therapeutic range (INR 2.0–3.0).

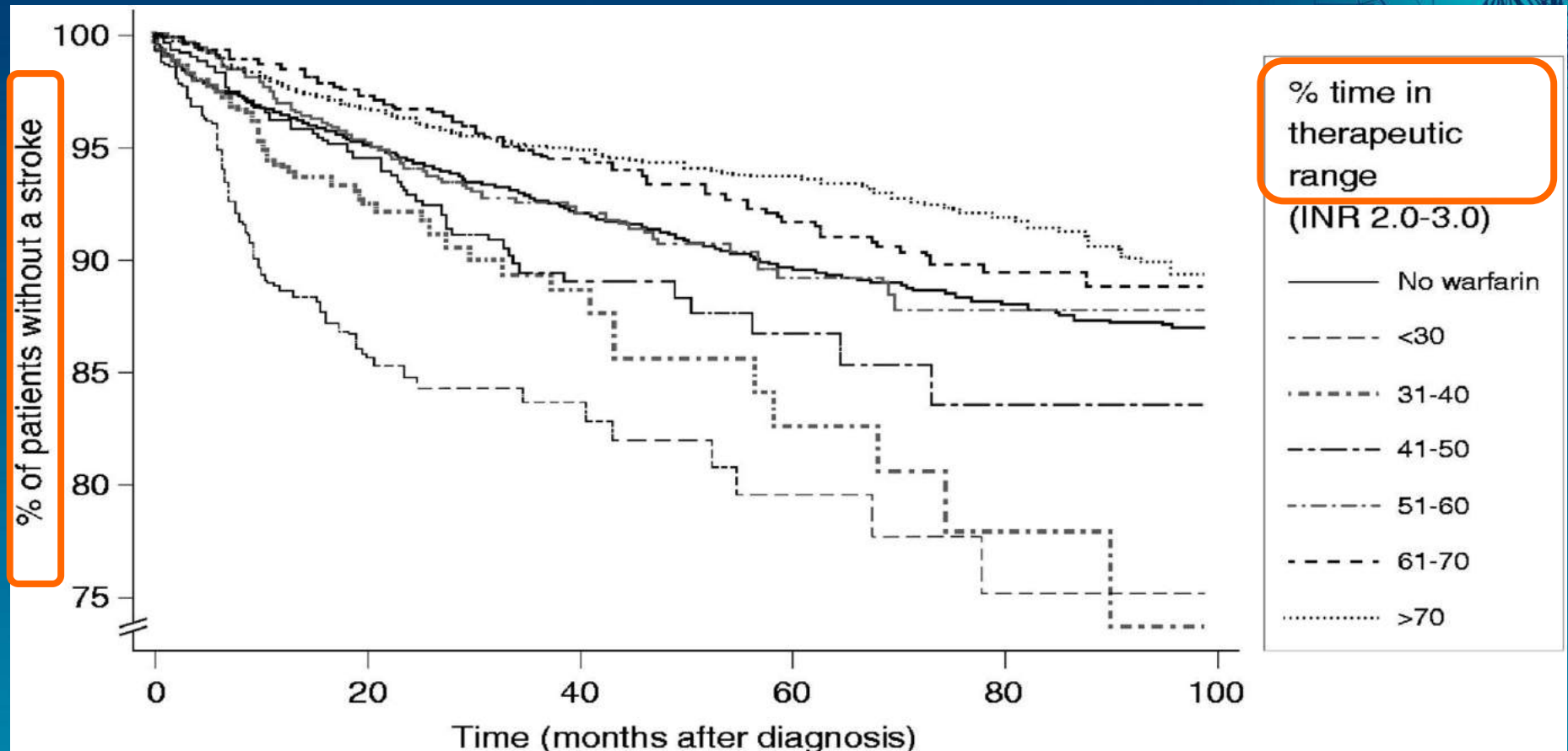


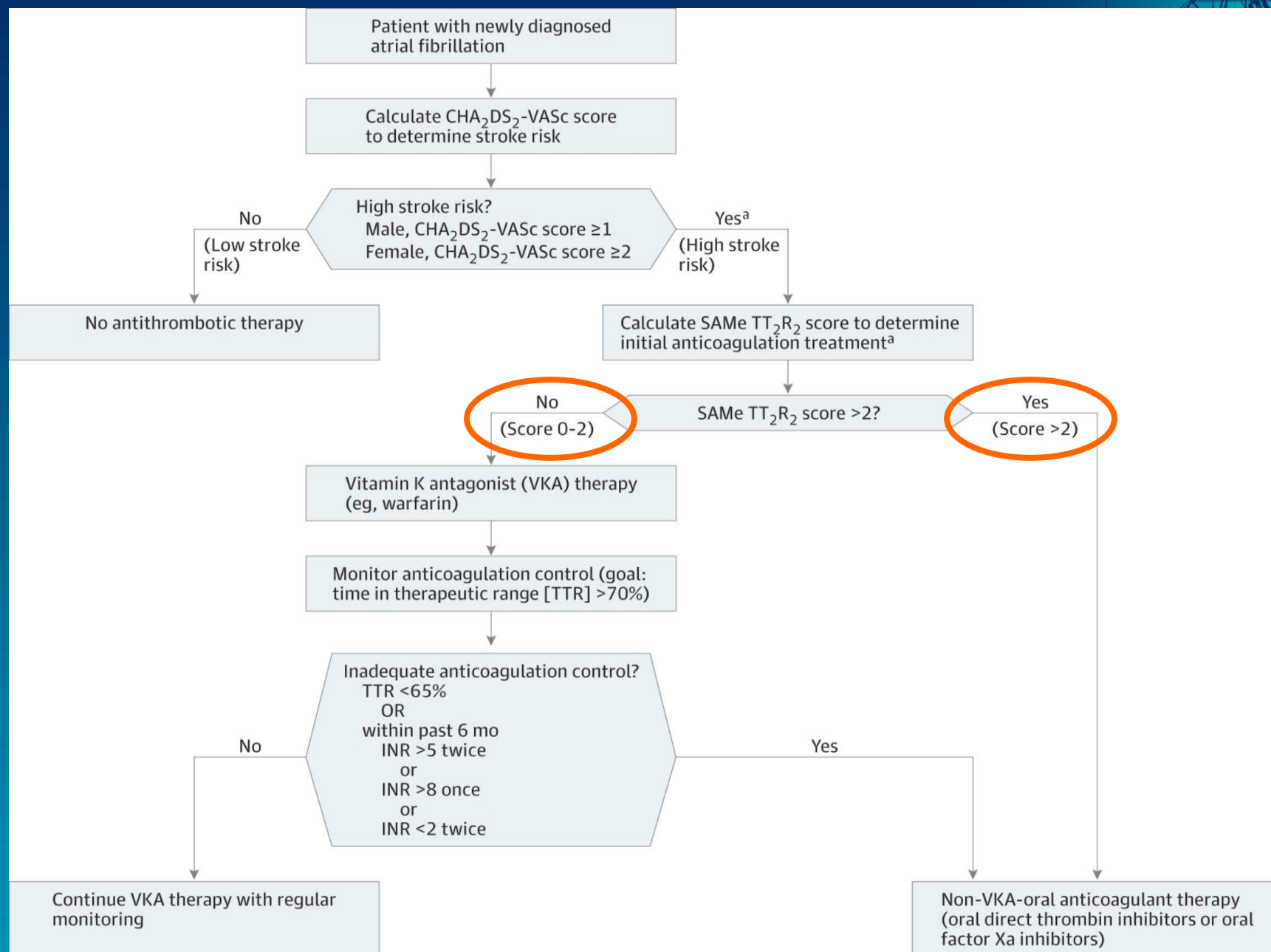
Table 5. Definition of the SAME-TT₂R₂ Score, Used to Aid Initial Decision Making Between Vitamin K Antagonist (With Good Quality Anticoagulation Control) and a Non-Vitamin K Antagonist Oral Anticoagulant^a

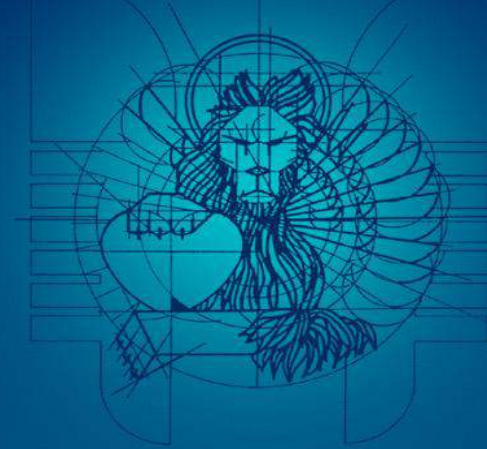
Definitions	Points
Sex (female)	1
Age (<60 y)	1
Medical history ^b	1
Treatment (interacting drugs, eg, amiodarone for rhythm control)	1
Tobacco use (within 2 y)	2
Race (not white)	2
Maximum points	8

^a The SAME-TT₂R₂ score is proposed as a means to help with decision making, to identify those newly diagnosed nonanticoagulated AF patients who have a probability of doing well while taking a vitamin K antagonist (VKA) (with SAME-TT₂R₂ score, 0-2) and achieve a time in therapeutic range (TTR) of at least 65% or 70%. In contrast, a SAME-TT₂R₂ score of more than 2 suggests that such patients are unlikely to achieve a good TTR while taking a VKA, and a non-VKA oral anticoagulant should be used upfront, without a "trial of warfarin" period.

^b Two of the following: hypertension, diabetes mellitus, coronary artery disease or myocardial infarctions, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, or hepatic or renal disease.

Algorithm for Risk Stratification and Selection of Anticoagulation Therapy for Stroke Prevention in AF





Stroke Risk Equivalent in Intermittent and Sustained AF

- Rate of ischaemic stroke 3.2% in intermittent AFib and 3.3% in sustained AFib

