Professor Martin Green lecture:

Stroke prevention in atrial fibrillation: Past, present and future

GREGORY Y H LIP MD FRCP (Lond Edin Glasg] FACC FESC

Professor of Cardiovascular Medicine, University of Birmingham, UK

Adjunct Professor of Cardiovascular Sciences, Thrombosis Research Unit, Aalborg University, Denmark

Visiting Professor of Haemostasis Thrombosis & Vascular Sciences, Aston University, Birmingham, UK

Visiting Professor of Cardiology, University of Belgrade, Serbia

Institute of Cardiovascular Sciences
City Hospital
Birmingham B18 7QH
England UK

.....

WINNER Cardiovascular Team of the Year BMJ AWARDS

University of Belgrade / Универзитет у Београду

AALBORG UNIVERSITY

Sandwell and West Birmingham Hospitals NHS NHS Trust

Aston University

Declaration of Interests

- Guideline membership/reviewing: ESC Guidelines on Atrial Fibrillation, 2010 and Focused Update, 2012; 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). Reviewer for various guidelines/position statements from ESC, EHRA, NICE etc.

- Steering Committees/trials: 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.

- Editorial Roles: Editor-in-Chief (clinical), Thrombosis & Haemostasis; Associate Editor, Europace; Guest Editor, Circulation, American Heart Journal.

- **Consultant/Advisor/Speaker:**
  - Consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo.
  - Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo

Professor Martin Green

Current director of the Postgraduate EP Fellowship program at the Heart Institute.

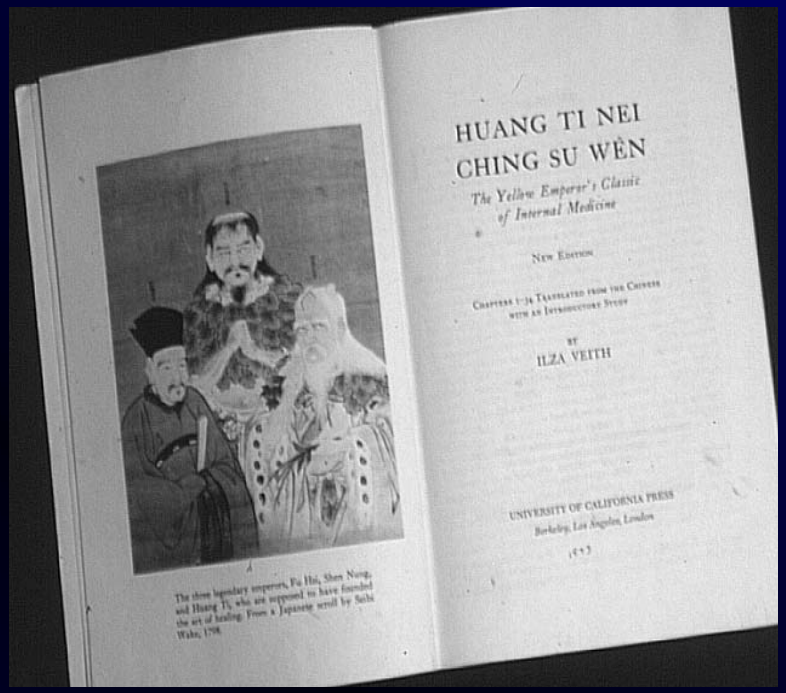
Trained in Internal Medicine at the University of Ottawa

In Maastricht, the Netherlands, to further training in Cardiac Electrophysiology under the direction of Professor Hein J. J. Wellens as a Fellow of the Medical Research Council of Canada.

Dr. Green start the Ottawa Arrhythmia Service in 1983. Since that time, the Arrhythmia Service has grown substantially and produced world class clinical arrhythmia care and research.

Perhaps the earliest description of AF

".....When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender [smaller than feeble, but still perceptible, thin like a silk thread], then the impulse of life is small....."



Huang Ti Nei Ching Su Wên

The Yellow Emperor's Classic of Internal Medicine

The legendary Emperor Physician is believed to have ruled China between 1696 and 2598 B.C.

William Withering
1741-1799
Birmingham

Digitalis purpurea 1785

‘An account of the foxglove and some of its medical uses: with practical remarks on Dropsy, and other diseases’

Stroke risk .. 'high risk' vs 'low risk' … and $CHADS_2$

'Artificial' risk stratification in AF evolved so that we could target 'high risk' patients for an inconvenient (and possibly dangerous) drug, warfarin

…. but a 'stroke risk factor' is a risk factor, and if found in association with AF, the patient will stroke

Stroke risk is a continuum, and the artificial division into low/moderate/high risk strata is …

- poorly predictive
- has no bearing on antithrombotic therapy use

The simple $CHADS_2$ score was derived from risk factors from non-VKA arms of historical trial cohorts (AF Investigators, SPAF)

- historical trials randomised <10% of patients screened
- simple, does not include many risk factors, poor predictive value
- classifies large % into 'moderate risk' category

Sweeney et al Br J Gen Pract 1995,45,153-158

Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score

Gage et al JAMA 2001;285:2864–70.

$CHADS_2$ **C**ongestive heart failure; **H**ypertension; **A**ge ≥75; **D**iabetes; **S**troke (2 points)

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.

†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

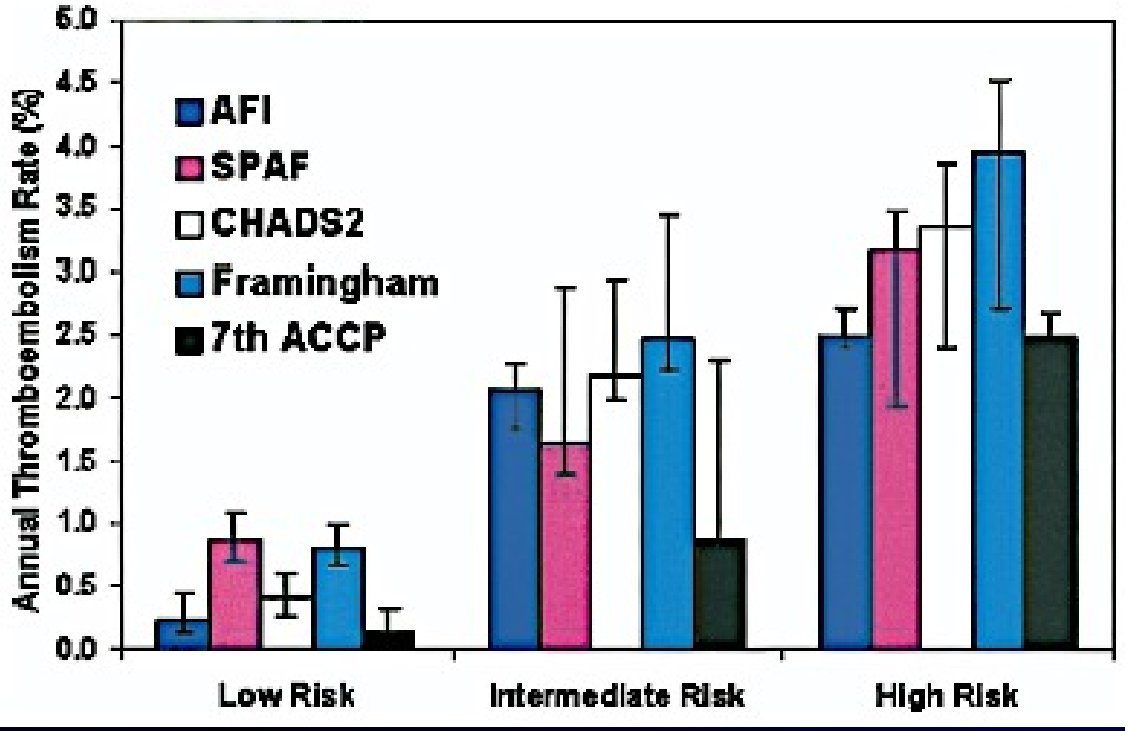
Risk factors were derived from the AFI and SPAF risk schemes, ie. non-warfarin arms of historical trial cohorts

The simple $CHADS_2$ helps identify 'high risk' patients to target for warfarin

Comparison of Risk Stratification Schemes to Predict Thromboembolism in Nonvalvular AF

Fang et al

J Am Coll Cardiol 2008;51:810–5

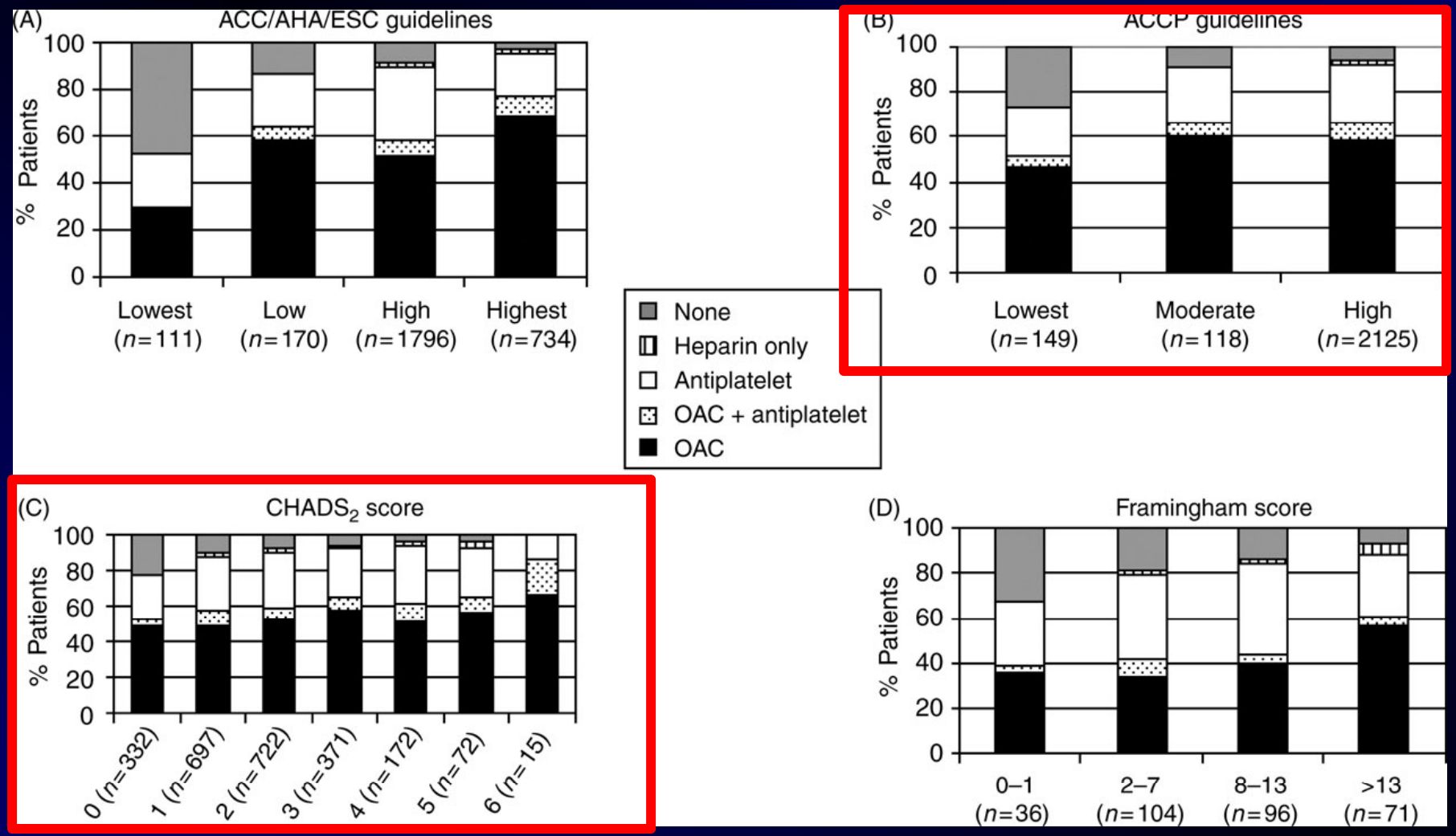


	Risk for Thromboembolism (%)			c-Statistic	
	Low	Intermediate	High	All Patients	Subgroup*
AFI	13.1	24.7	62.3	0.56	0.61
SPAF	27.7	28.5	43.8	0.60	0.65
$CHADS_2$	18.8	61.2	20.1	0.58	0.67
Framingham	37.1	46.6	16.4	0.62	0.69
7th ACCP	11.7	7.9	80.4	0.56	0.60

*Subgroup of 5,588 patients not on warfarin at baseline and with continuous follow-up off of warfarin for at least 12 months.

Antithrombotic treatment in real-life AF patients: the Euro Heart Survey on Atrial Fibrillation

Nieuwlaat et al Eur Heart J 2006; 27, 3018–3026



Antithrombotic drug prescription per risk category according to the ACC/AHA/ESC guidelines (A), ACCP guidelines (B), $CHADS_2$ score (C), and the Framingham score (D).

Validation of the $CHADS_2$ clinical prediction rule to predict ischaemic stroke: A systematic review and meta-analysis

Keogh et al Thromb Haemostat 2011; doi:10.1160/TH11-02-0061

$CHADS_2$ score	No. of studies	Sensitivity (95% CI)	Variance logit (sensitivity)	Specificity (95% CI)	Variance logit (specificity)
≥1	6	0.92 (0.82–0.96)	0.31	0.12 (0.06–0.24)	0.85
≥2	4	0.79 (0.64–0.89)	0.01	0.42 (0.24–0.63)	0.74
≥3	6	0.50 (0.37–0.63)	0.88	0.77 (0.59–0.88)	0.99
≥4	5	0.33 (0.21–0.47)	0.00	0.96 (0.66–0.10)	7.28

*There was insufficient data to examine the $CHADS_2$ score for ≥5 or ≥6.

'….. the pooled c statistic and calibration analysis suggests minimal clinical utility of … $CHADS_2$ in predicting ischaemic stroke across all risk strata'

…… Further validation of $CHADS_2$ should perhaps be undertaken.

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 $CHADS_2$ Risk Scores by vWf level

…

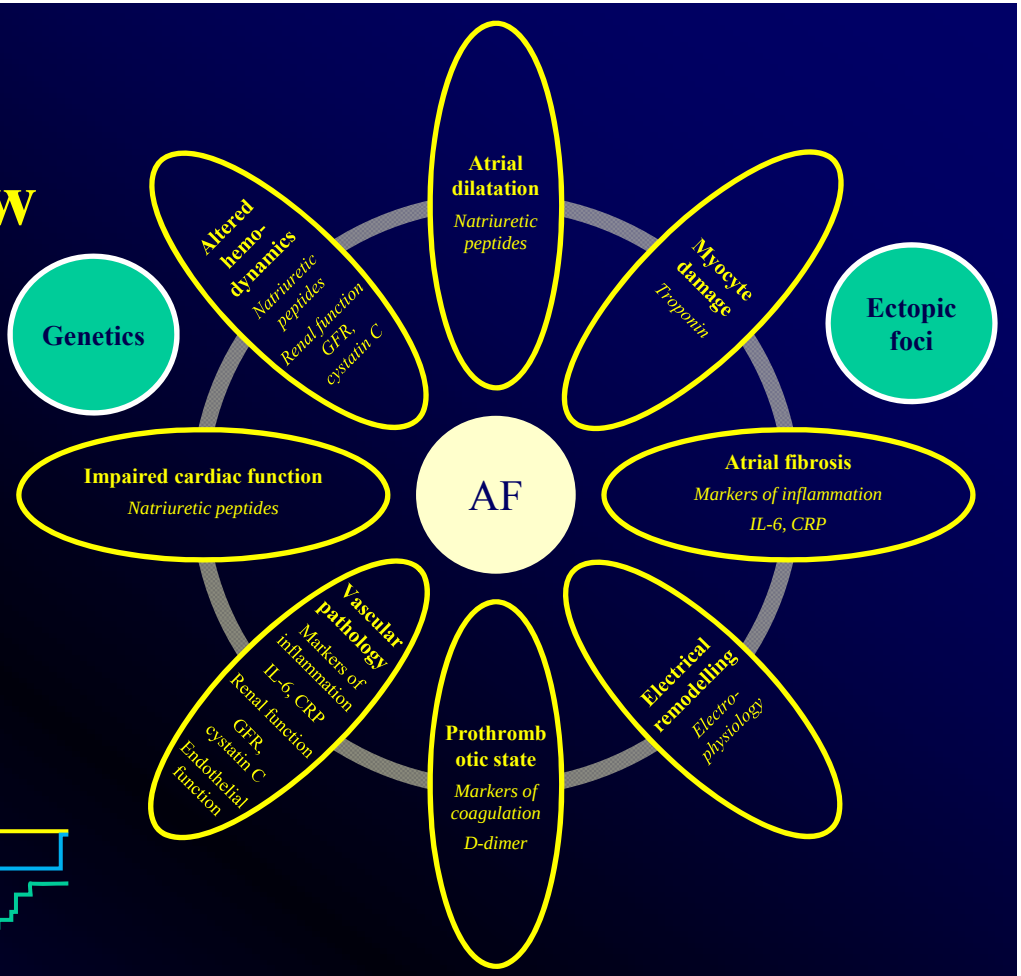
high plasma vWf level was defined as the top tertile (>158 IU/dL) of vWf levels in the study cohort. Low plasma vWf levels were defined as <158 IU/dL

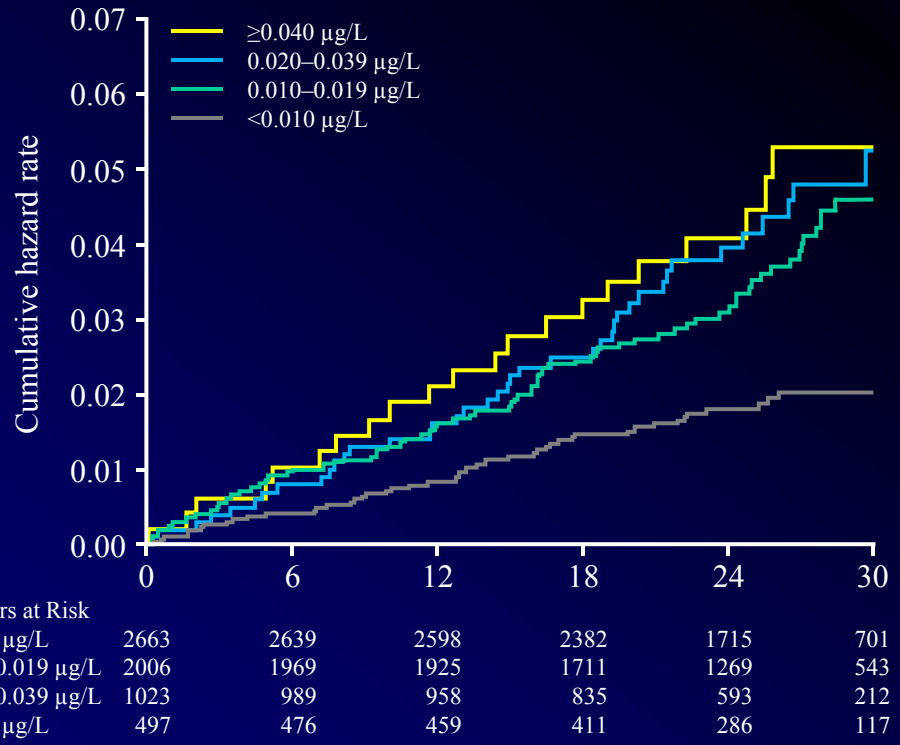
Biomarkers in atrial fibrillation: a clinical review

Hijazi et al Eur Heart J 2013

Various biomarkers have been used to aid risk stratification in AF ..

- D-dimer, vWf, BNP, CRP, troponin, etc





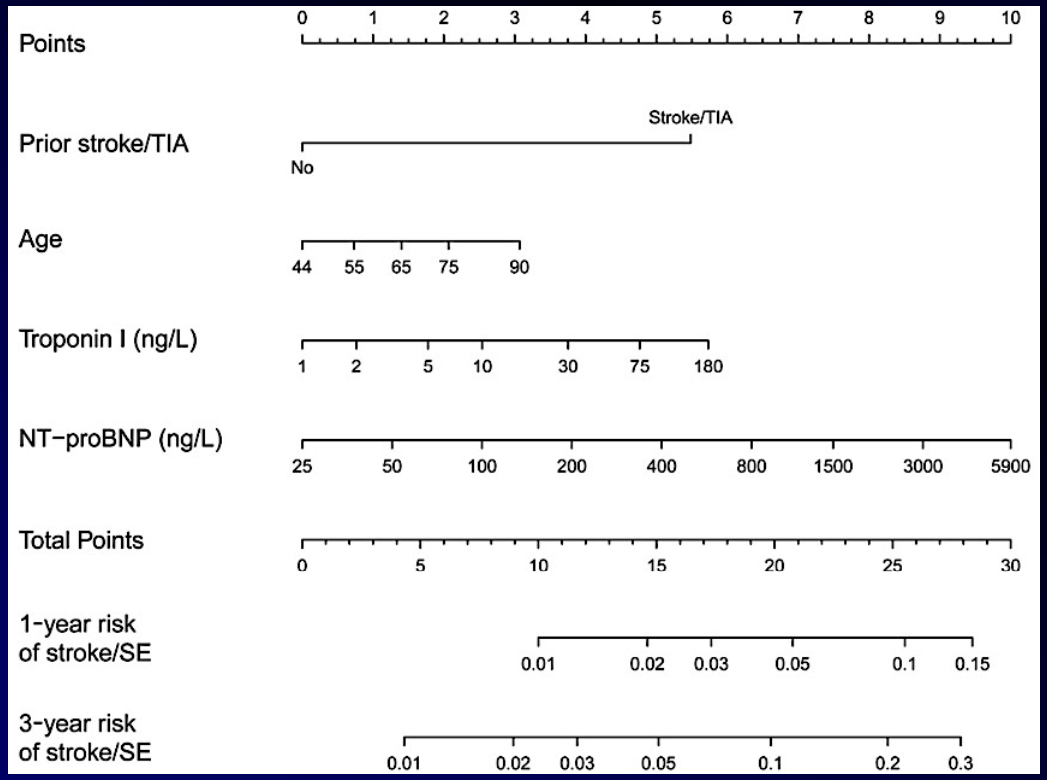
Cumulative hazard rates for stroke or systemic embolism, according to Troponin I levels at randomization in *an anticoagulated cohort* from RE-LY trial

Hijazi et al Circulation 2012;125:1605-16.

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

	Full cohort
Derivation cohort	
ABC-stroke (troponin I)	0.68 (0.65, 0.71)
ABC-stroke (troponin T)	0.67 (0.65, 0.70)
CHA_2DS_2-VASc	0.62 (0.60, 0.65)
Validation cohort	
ABC-stroke (troponin T)	0.66 (0.58, 0.74)
CHA_2DS_2-VASc	0.58 (0.49, 0.67)



- 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.

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?

Gregory Y.H. Lip*

University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, UK

Received 2 October 2012; revised 3 November 2012; accepted 25 November 2012

'….. 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'

The CHA_2DS_2-VASc score

Lip et al Chest. 2010;137:263-72

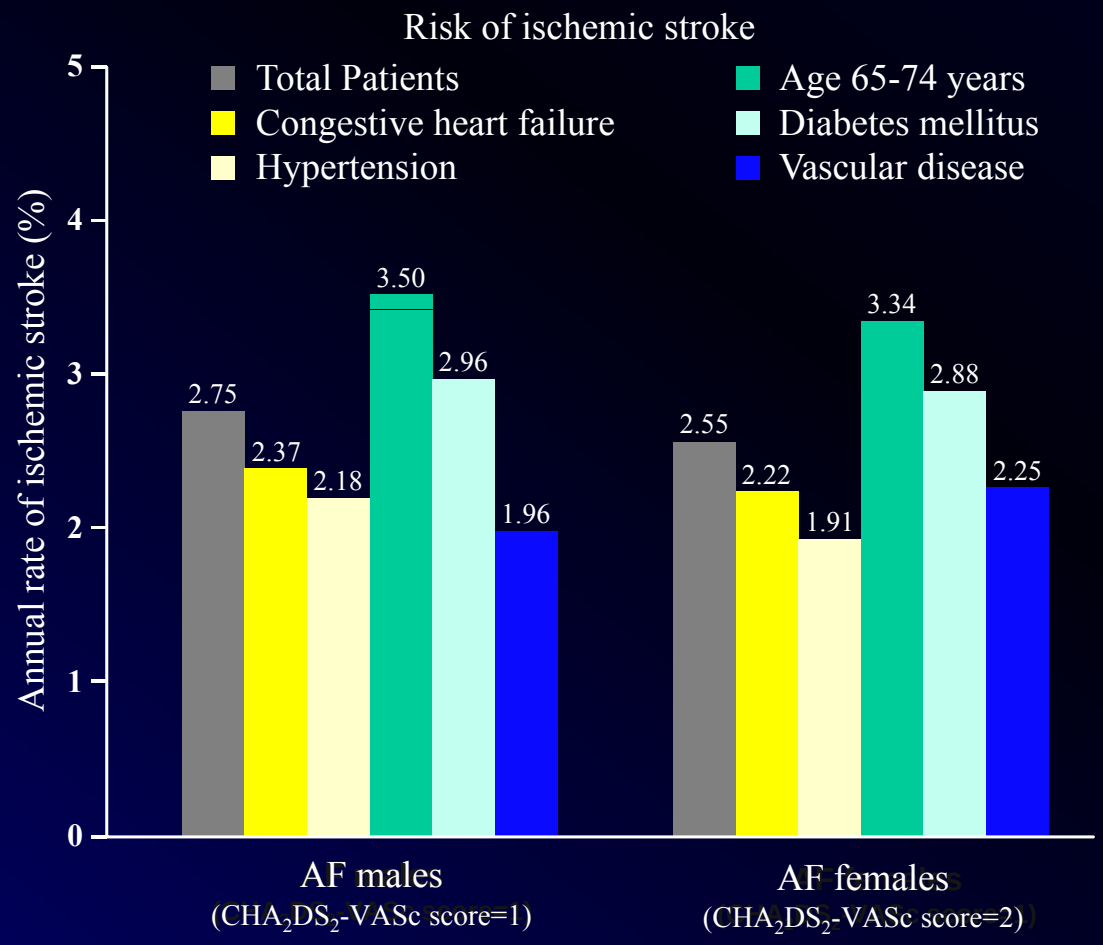
Camm, Kirchhof, Lip et al
Eur Heart J 2010; 31, 2369–2429

a) Risk factors for stroke and thromboembolism in non-valvular AF	
'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke, TIA or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%] Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease*

Stroke risk factors	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior MI, PAD, or aortic plaque]	1
Aged 65–74 years	1
Sex category [i.e. female gender]	1

Is OAC Necessary in AF Patients with a CHA_2DS_2-VASc Score=1 (males) or 2 (females)? A nationwide cohort study

Chao, Liu … Lip, Chen. JACC 2015 ;65(7):635-42. Presented at ESC 2014



OAC should be considered for AF patients with 1 additional stroke risk factor (ie. CHA_2DS_2-VASc score of 1 (males) or 2 (females))

Ischaemic stroke rates in non-anticoagulated male and female patients with 1 additional stroke risk factor

Event rates (per 100 person-years) of ischemic stroke/SE/TIA in 980 AF patients with prior vascular disease stratified according to type

Nielsen … Lip. Can J Cardiol. 2015 Jun;31(6):820.e9-10.

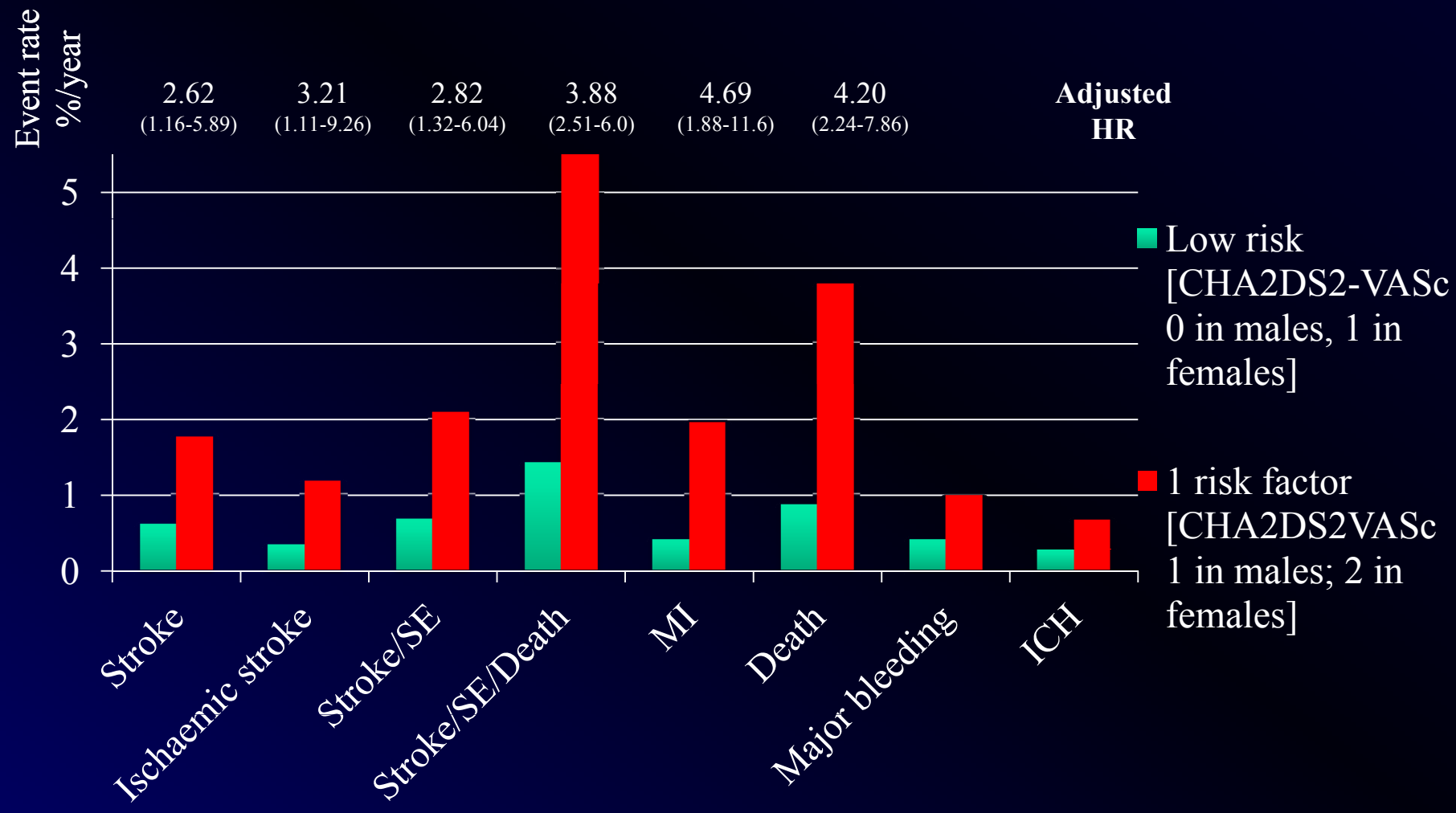
Type of vascular disease	No of patients	No of events / person-time	Event rate (95% CI)
MI	651	12/490	2.5 (1.4-4.3)
Peripheral artery disesae	294	6/201	3.0 (1.3-6.7)
Both MI and PAD	35	3/20	15.0 (4.8-46.4)

- High stroke rate of 4.85 per 100 person-years in AF patients with vascular disease as a single risk factor.

Compared to low risk CHA_2DS_2-VASc (that is, score 0 (male) or 1 (female)) as a reference population, the hazard attributable to vascular disease as a single risk factor resulted in a crude HR of 2.7 (95%CI 1.7-4.2).

Event rates for different outcomes for non-anticoagulated AF patients with less than 2 Non-Gender Related stroke risk factors

Fauchier … Lip. Stroke 2016 DOI: 10.1161/STROKEAHA.116.013253



Stroke and TE event rates in AF according to different guideline Rx thresholds

Nielsen … Lip.
Sci Rep 2016; **6**, 27410;
doi: 10.1038/srep27410

	U.S. guideline recommendations†		European guideline recommendations‡	
	Women	Men	Women	Men
CHA_2DS_2-VASc =0	N/A*	No therapy	N/A*	No therapy
CHA_2DS_2-VASc =1	Oral anticoagulation, aspirin, or no therapy		No therapy	Oral anticoagulation
CHA_2DS_2-VASc ≥2	Oral anticoagulation		Oral anticoagulation	

* Women cannot score 0, as female sex triggers 1 point in the CHA_2DS_2-VASc score

†The American College of Cardiology, the American Heart Associations, and the Heart Rhythm Society (ACC/AHA/HRS) ‡European Society of Cardiology (ESC). N/A: Not available.

Thromboembolic event rates in relation to different methodological approaches and stratified according to cut-off values of stroke risk based on CHA_2DS_2-VASc

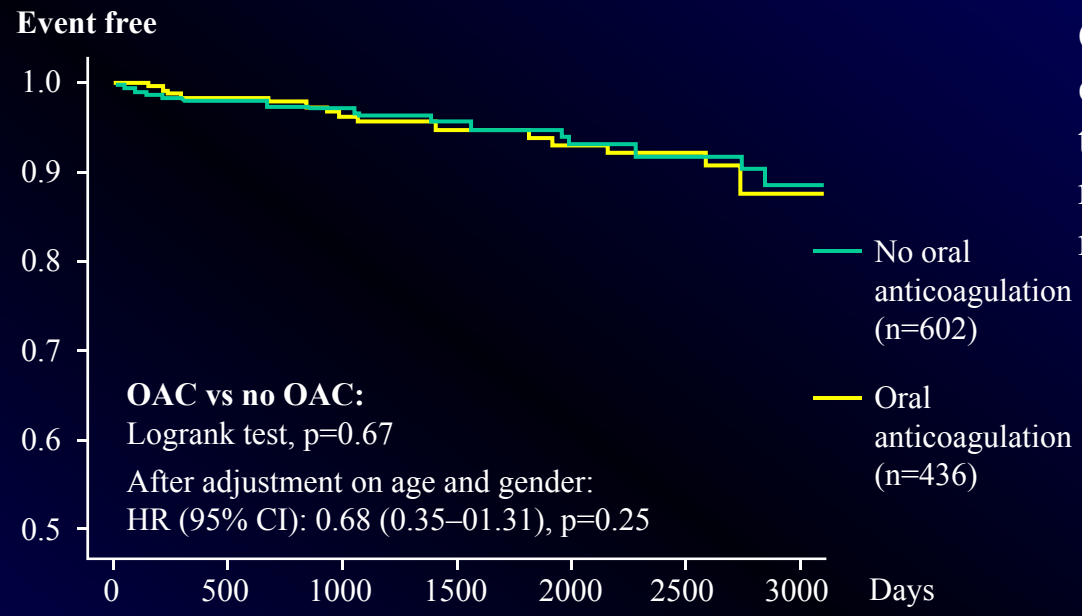
Risk stratification	CHA_2DS_2-VASc score	Formal rate assessment			Conditioning on the future approach			Censoring observation at oral anticoagulant treatment		
		Events	Person-years	Rate/100 person-years	Events	Person-years	Rate/100 person-years	Events	Person-years	Rate/100 person-years
Truly low risk	0 (1 for females)	688	114,504	0.60	168	56,053	0.30	400	73,873	0.54
European treatment threshold	1 (males)	812	61,773	1.31	200	17,067	1.17	402	26,324	1.53
U.S. treatment threshold	2	2,245	114,034	1.97	792	40,576	1.95	1,305	55,920	2.33
High risk	>2	12,737	288,944	4.41	6375	129,572	4.92	8,569	156,032	5.49

Thromboembolic event rates differed markedly in non-anticoagulated AF patients according to guideline treatment thresholds.

Choice of analysis methodological approach has implications … we recommend using the censoring approach for event rate estimation among AF patients not on treatment.

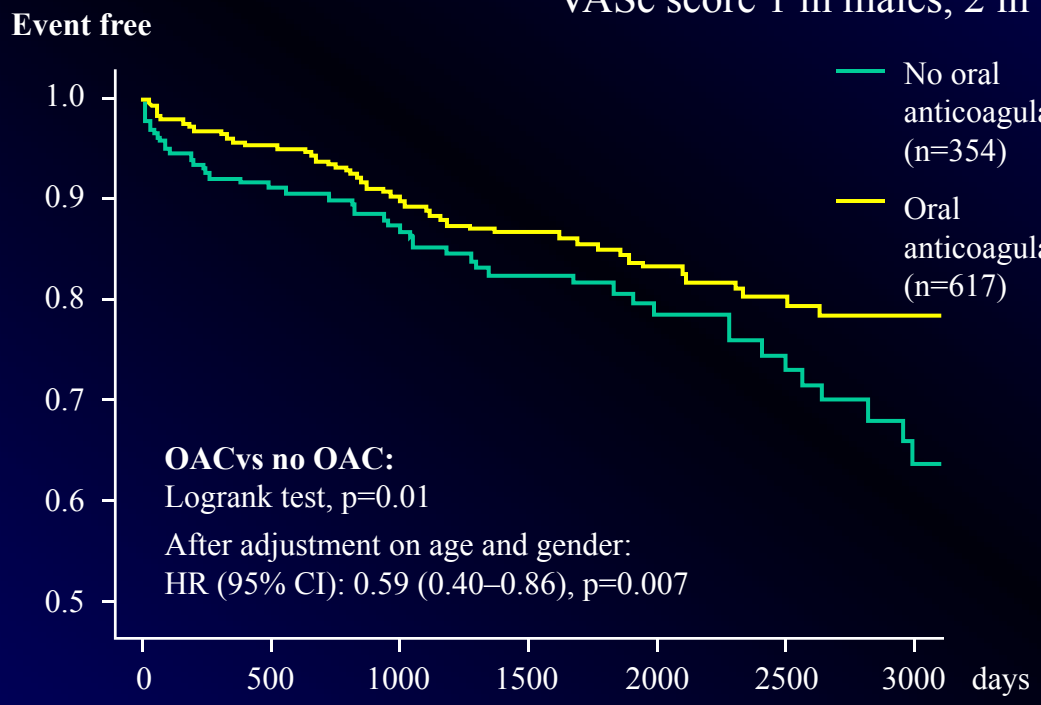
OAC and the risk of stroke or death in patients with AF and 0-1 stroke risk factors: the Loire Valley AF Project

Fauchier … Lip, Chest 2015 doi 10.1016/j.chest.2015.09.009



Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with low risk of stroke (CHA_2DS_2-VASc score 0 in males, or 1 in females)

Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with 1 additional risk factor (CHA_2DS_2-VASc score 1 in males, 2 in females)



Net Clinical Benefit analysis of stroke prevention strategy for AF patients with 1 NGR stroke risk factor (CHA_2DS_2VASc 1 in males, 2 in females)

Fauchier … Lip. Stroke 2016 DOI: 10.1161/STROKEAHA.116.013253

Stroke prevention strategy	Net Clinical Benefit, %/year (95%CI) according to Singer et al.	Net Clinical Benefit, %/year (95%CI) according to Connolly et al.
Compared to no antithrombotic therapy		
Anti-platelet drugs (and no VKA)	-0.13 (-1.06 to -0.02)	-0.72 (-1.50 to -0.34)
VKA	0.30 (0.15-0.61)	1.42 (1.01-1.99)
Compared to anti-platelet drugs (and no VKA)		
VKA	0.43 (0.24-0.78)	2.14 (1.62-2.82)

NCB according to Singer et al = (ischemic stroke rate on no treatment minus ischemic stroke rate on anti-thrombotic therapies) – 1.5x (ICH rate on anti-thrombotic therapies minus ICH rate on no treatment).
NCB according to Connolly et al= weighted sum of rate differences ΔR = Rate not treated – Rate treated:w1 * ΔRischemic stroke + w2 * ΔRICH + w3 * ΔRmajor bleeding + w4 * ΔRMI.
ICH=intracerebral hemorrhage,major bleeding =major extracranial bleeding, MI= myocardial infarction, VKA= vitamin K antagonist weights w1=1, w2=3.08, w3=0.67, w4=0.95.

Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA_2DS_2-VASc score

A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy

Gregory Y. H. Lip[1,2]; Flemming Skjøth[1,3]; Peter B. Nielsen[1,4]; Torben Bjerregaard Larsen[1,4]

[1]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark; [2]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [3]Unit of Clinical Biostatistics and Bioinformatics, Aalborg University Hospital, Aalborg, Denmark; [4]Department of Cardiology, AF Study group, Aalborg University Hospital, Aalborg, Denmark

Summary

Oral anticoagulation (OAC) to prevent stroke has to be balanced against the potential harm of serious bleeding, especially intracranial haemorrhage (ICH). We determined the net clinical benefit (NCB) balancing effectiveness and safety of no antithrombotic therapy, aspirin and warfarin in AF patients with none or one stroke risk factor. Using Danish registries, we determined NCB using various definitions intrinsic to our cohort (Danish weights at 1 and 5 year follow-up), with risk weights which were derived from the hazard ratio (HR) of death following an event, relative to HR of death after ischaemic stroke. When aspirin was compared to no treatment, NCB was neutral or negative for both risk strata. For warfarin vs no treatment, NCB using Danish weights was neutral where no risk factors were present and using five years follow-up. For one stroke risk factor, NCB was positive for warfarin vs no treatment, for one year and five year follow-up. For warfarin vs aspirin use in patients with no risk factors, NCB was positive with one year follow-up, but neutral with five year follow-up. With one risk factor, NCB was generally positive for warfarin vs aspirin. In conclusion, we show a positive overall advantage (i.e. positive NCB) of effective stroke prevention with OAC, compared to no therapy or aspirin with one additional stroke risk factor, using Danish weights. 'Low risk' AF patients with no additional stroke risk factors (i.e.CHA_2DS_2-VASc 0 in males, 1 in females) do not derive any advantage (neutral or negative NCB) with aspirin, nor with warfarin therapy in the long run.

Keywords

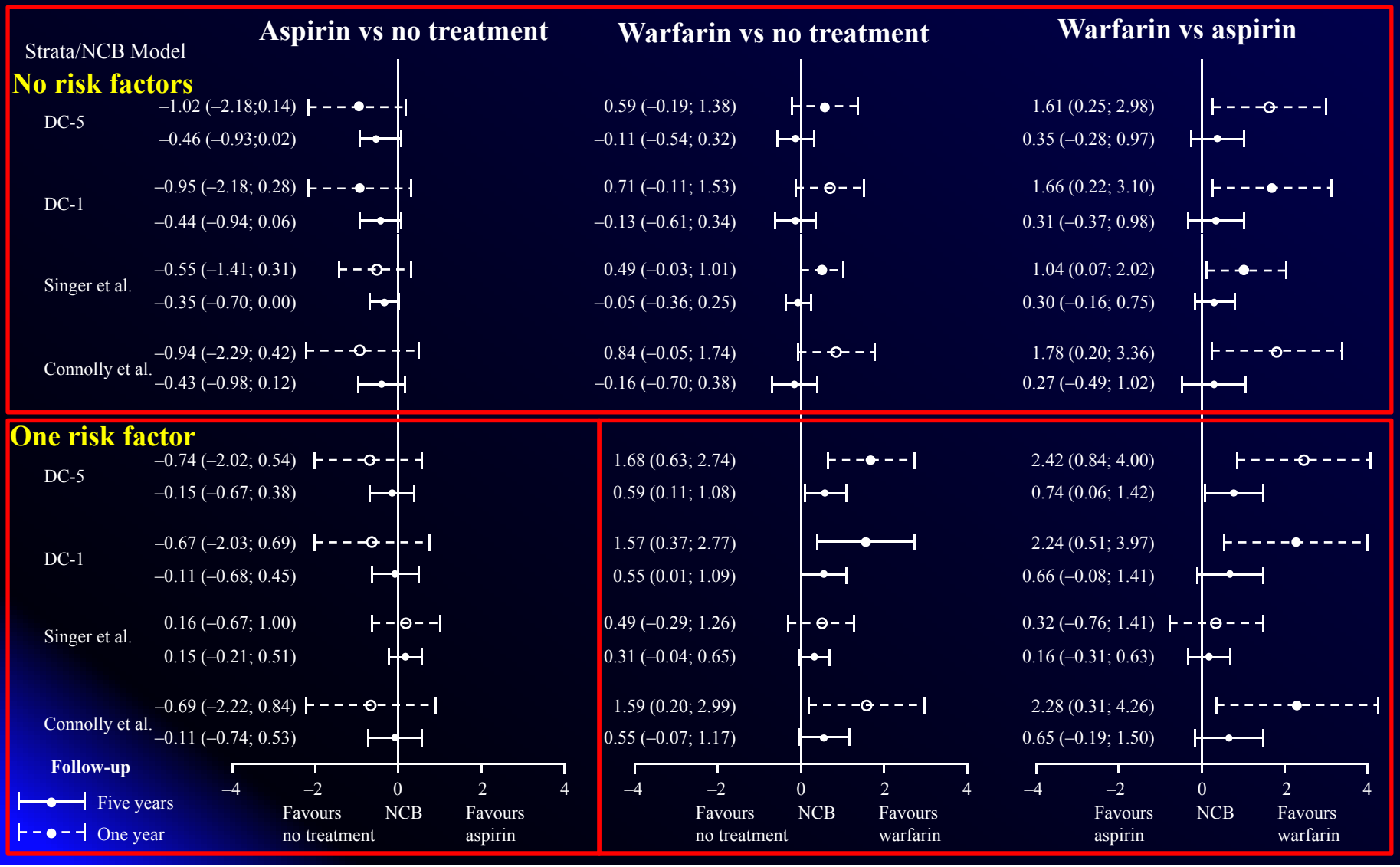
Net clinical benefit, mortality, stroke, bleeding

Thromb Haemostat 2015; http://dx.doi.org/10.1160/TH15-07-0565

Non-valvular AF patients with none or one additional risk factor of the CHA_2DS_2-VASc score

A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy

Lip et al Thromb Haemostat 2015; http://dx.doi.org/10.1160/TH15-07-0565



$CHADS_2$ and CHA_2DS_2-VASc scores for predicting ischemic stroke in Asian patients with AF

Xiong … Lip, Int J Cardiol 2015; ;195:237-242

Low risk

	$CHADS_2$=0		CHA_2DS_2-VASc=0			
	Events	Total	Events	Total	Weight	Risk ratio, M-H, fixed, 95% CI
Chao TF 2014	17	302	5	78	11.5%	0.88 (0.33-2.31)
Guo YT 2013	0	88	0	52		Not estimable
Komatsu T 2014	1	115	0	76	0.9%	1.99 (0.08-48.25)
Lin YL 2011	47	2335	10	659	22.5%	1.33 (0.67-2.61)
Siu CW 2014	185	1012	25	292	56.0%	2.14 (1.44-3.18)
Suzuki S 2015	9	1090	5	617	9.2%	1.02 (0.34-3.03)
Total (95% CI)		4942		1774	100.0%	1.71 (1.26-2.31)

0.01 0.1 1 10 100

$CHADS_2$ CHA_2DS_2-VASc

High risk

	$CHADS_2$≥2		CHA_2DS_2-VASc≥2			
	Events	Total	Events	Total	Weight	Risk ratio, M-H, random, 95% CI
Chao TF 2014	1101	9590	1188	10573	25.6%	1.02 (0.95-1.10)
Guo YT 2013	27	591	32	719	7.1%	1.03 (0.62-1.69)
Komatsu T 2014	32	103	35	196	9.2%	1.74 (1.15-2.64)
Lin YL 2011	279	2681	409	5793	22.0%	1.47 (1.27-1.70)
Siu CW 2014	1172	4854	1665	6933	26.1%	1.01 (0.94-1.07)
Suzuki S 2015	44	1329	58	2269	10.1%	1.30 (0.88-1.91)
Total (95% CI)		19148		26483	100%	1.19 (1.02-1.38)

0.1 0.2 0.5 1 2 5 10

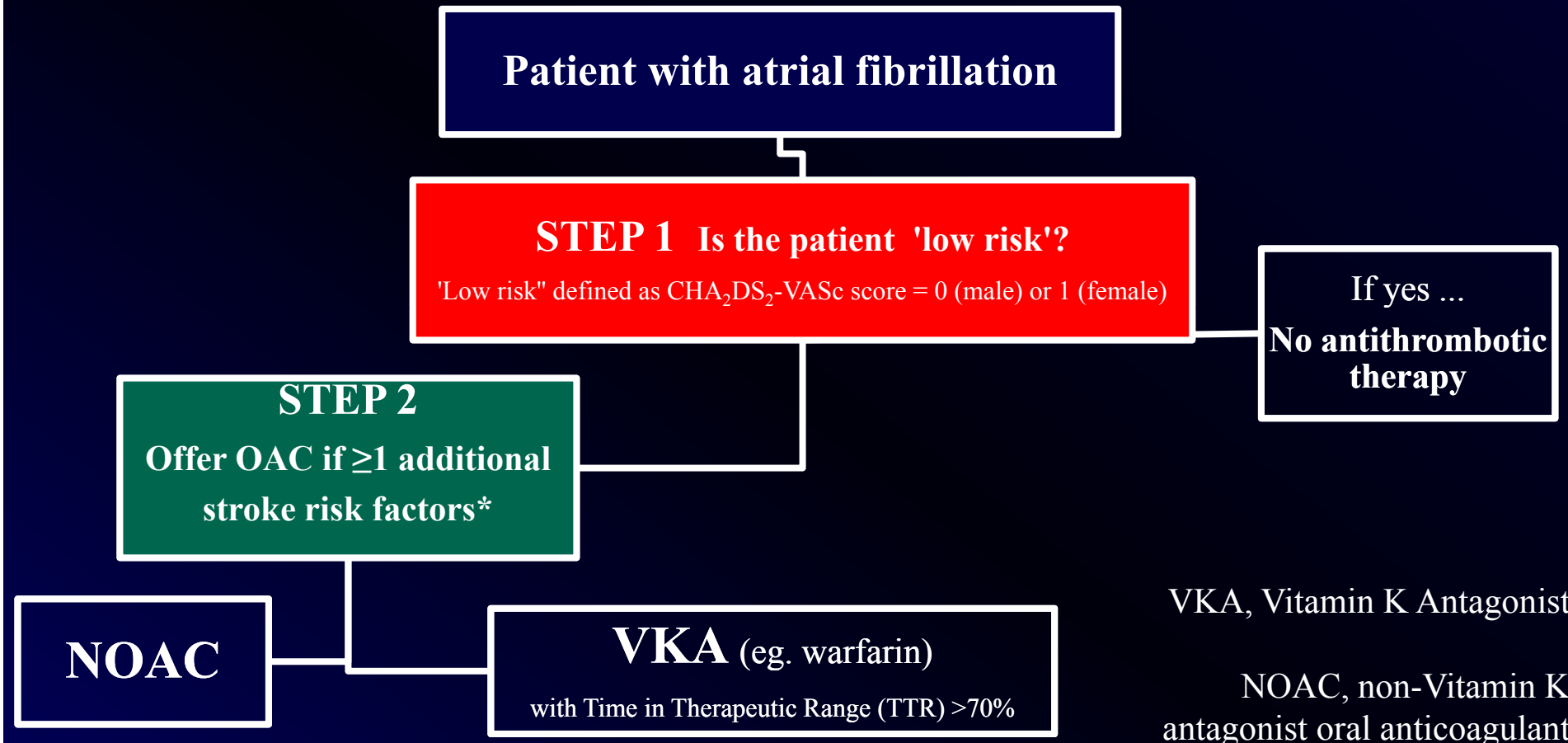
$CHADS_2$ CHA_2DS_2-VASc

CHA_2DS_2-VASc score was superior to $CHADS_2$ score in identifying 'low risk' Asians patients with AF

Rather than a categorical approach, Asian guidelines should adopt a 2-step approach, by initially identifying truly low risk patients, following which stroke prevention can be offered to those with ≥1 additional stroke risk factors.

Risk stratification and thromboprophylaxis made easy

Lip and Lane Circ J 2014 June; Griffiths and Lip Circulation 2014;130(21):1837-9



VKA, Vitamin K Antagonist

NOAC, non-Vitamin K antagonist oral anticoagulant

* Use the HAS-BLED score to identify patients at 'high risk' of bleeding for more careful review and followup, and to address reversible risk factors for bleeding. A high HAS-BLED score (≥3) does not preclude use of OAC, and may help with NOAC dose selection

Illustrative case

50 year old man with uncontrolled hypertension (BP>180/110mmHg), prior stroke, labile INRs on warfarin (TTR 40%), concomitant use of NSAIDs (Cox-2 inhibitors), abnormal liver function and excess alcohol intake

Assess bleeding risk

ORBIT score=0
Low risk

ATRIA score=1
Low risk

Low risk, so 'no action'?

$HEMORR_2HAGES$ score =4
High risk

HAS-BLED score =6
High risk

'High risk' HAS-BLED score

- Not a reason to withold OAC
- Flags up the patient for more regular review and more careful followup
- Address the potentially reversible bleeding risk factors
  - In this case, treat the uncontrolled hypertension, improve TTR, reduce/minimise NSAID use and alcohol intake

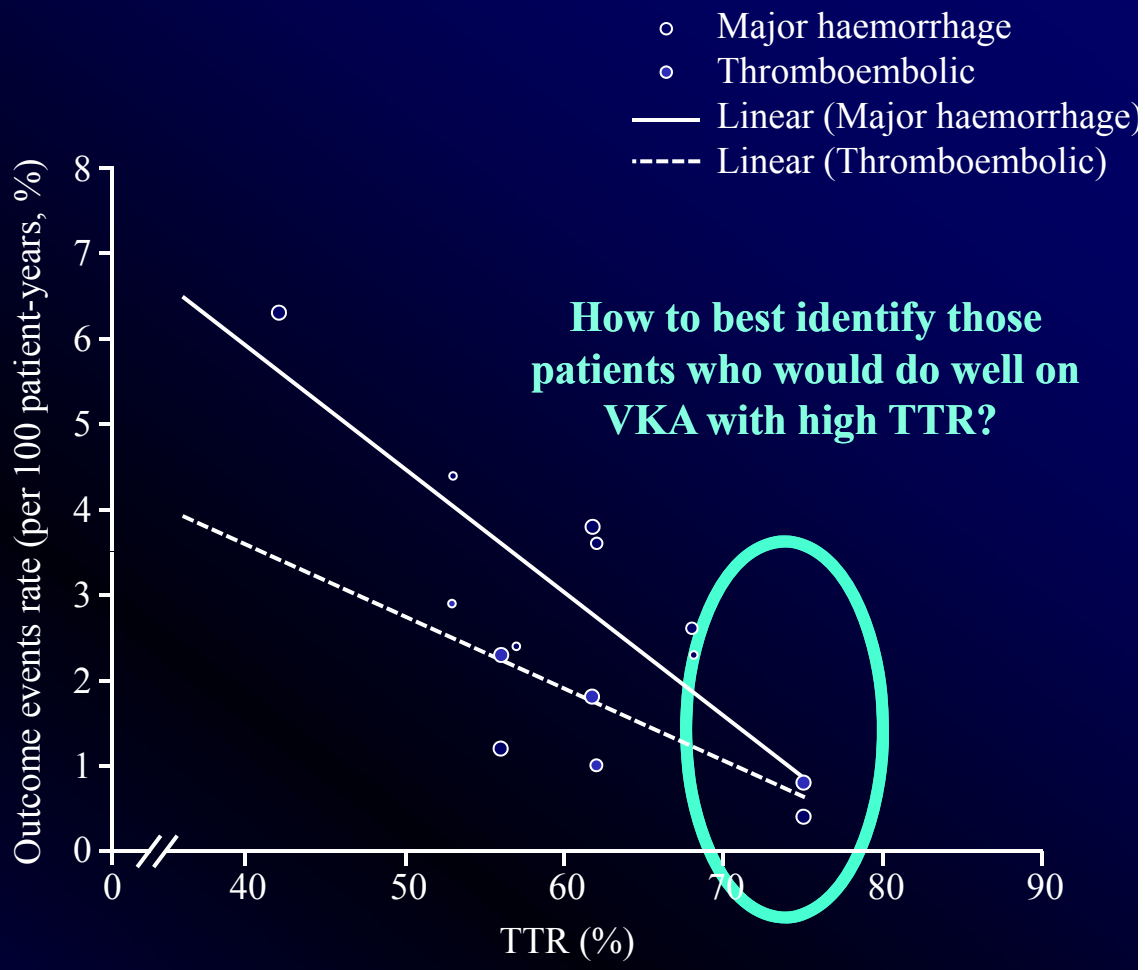
[Recommendations as per 2012 ESC and 2014 NICE guidelines]

Assessing bleeding risk in a patient with atrial fibrillation, and subsequent management

Lip and Lane, Eur Heart J; 2015 doi:10.1093/eurheartj/ehv415

Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation

Wan et al
Circ Cardiovasc Qual Outcomes. 2008;1:84-91

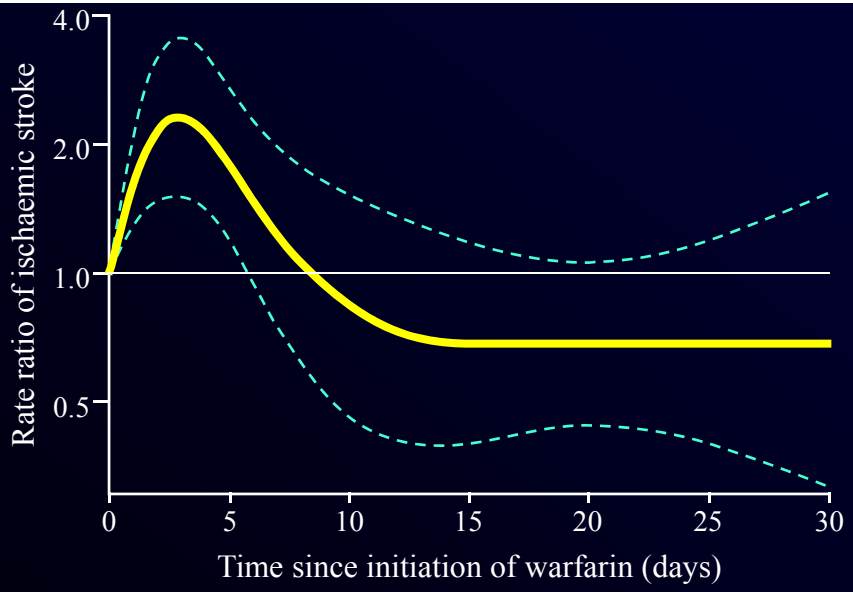


For retrospective studies, a 6.9% improvement in the TTR significantly reduced major hemorrhage by 1 event per 100 patient-years of treatment (95% CI, 0.29 to 1.71 events).

TTR negatively correlated with major hemorrhage (r=-0.59; P=0.002) and thromboembolic rates (r=-0.59;P=0.01).

Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes

Azoulay et al
Eur Heart J 2014;35(28):1881–7



Smooth cubic spline curve of the adjusted rate ratio of ischaemic stroke (solid line) and 95% confidence limits (dashed lines) as a function of the time since initiation of warfarin.

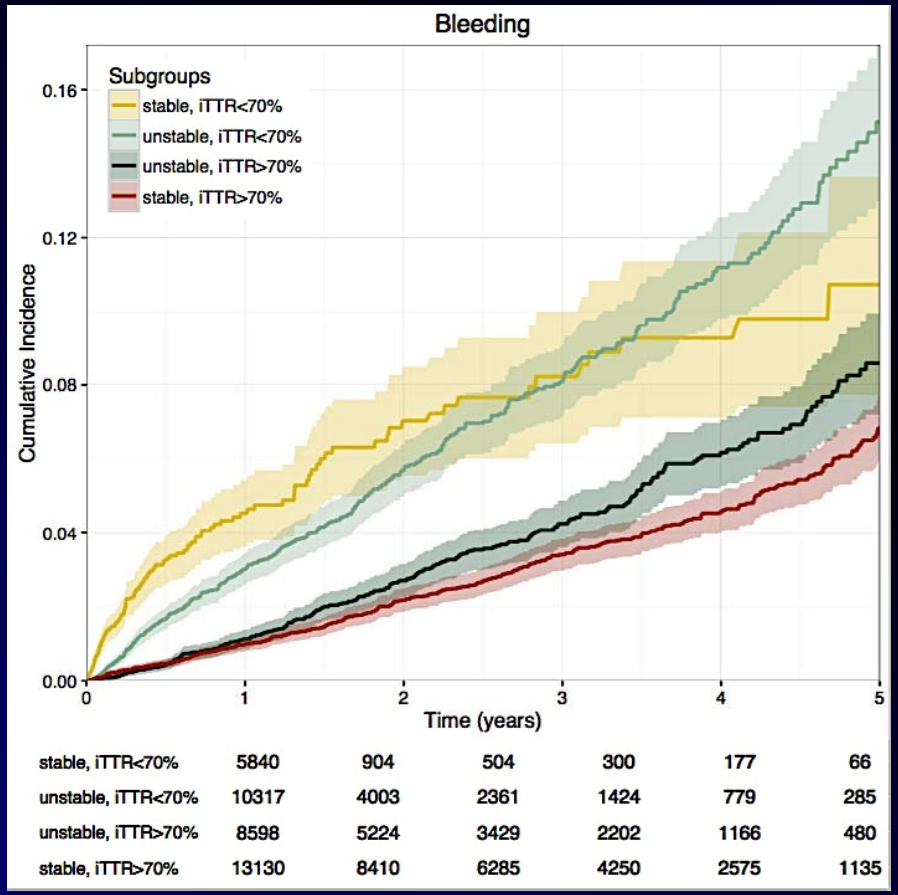
Timing of warfarin initiation and the risk of ischaemic stroke

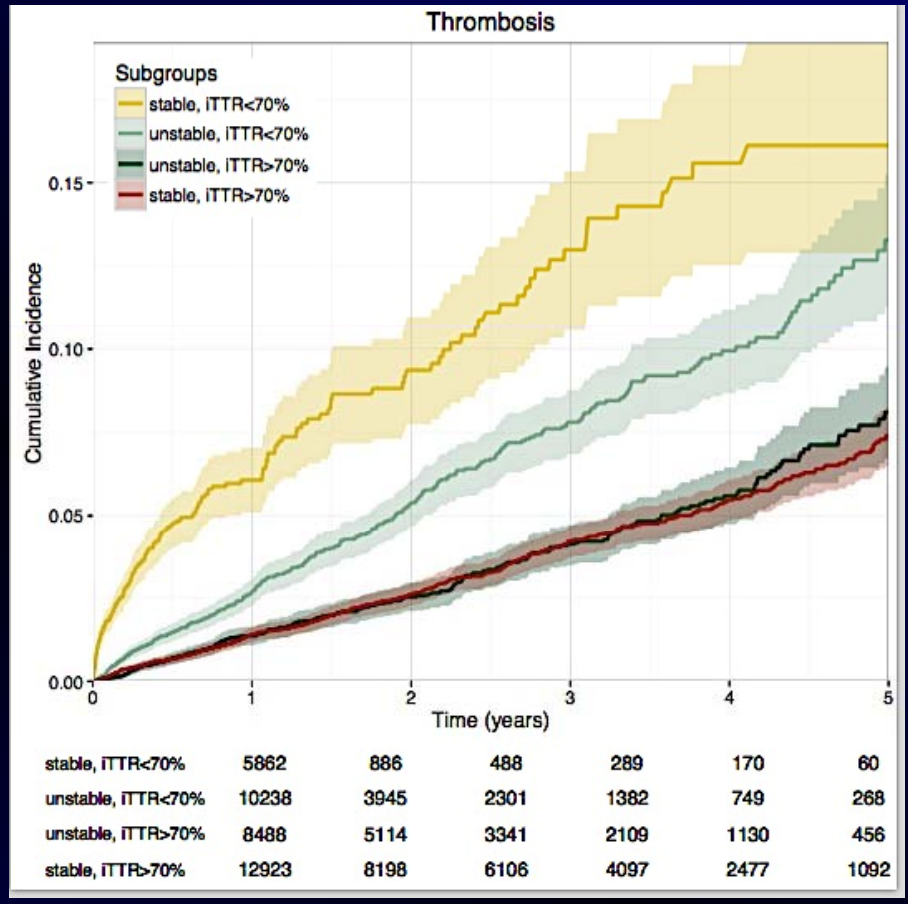
Current use of warfarin monotherapy	Cases (n=5519)	Controls[a] (n=55,022)	Crude RR	Adjusted RR (95% CI)[b]
No use of any antithrombotic therapy for at least 1 year, n (%)	1513 (27.4)	15499 (28.2)	1.00	1.00 (reference)
Time since initiation of warfarin, n (%)				
≤30 days	117 (2.1)	732 (1.3)	1.74	1.71 (1.39−2.12)
31–90 days	27 (0.5)	544 (1.0)	0.52	0.50 (0.34−0.75)
≥90 days	610 (11.1)	10145 (18.4)	0.57	0.55 (0.49−0.61)

[a] Cases and controls were matched on age, sex and date of atrial fibrillation diagnosis, and time since AF diagnosis.
[b] Adjusted for excessive alcohol use, smoking status, obesity, $CHADS_2$ score, PAD, MI, previous cancer, prior bleeds, VTE, valvular disease, and use of ACE inhibitors, ARBs, antidepressants, antipsychotics, NSAIDs, and statins.

Outcomes in a Contemporary Warfarin-Treated Population With Atrial Fibrillation

Björck … Lip et al JAMA Cardiology 2016 doi:10.1001/jamacardio.2016.0199





N=29146

Stable equals low INR variability (□□mean INR variability); unstable, high INR variability (<mean INR variability).

Well-managed warfarin therapy is associated with a low risk of complications

Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin: The SAMe-TT_2R_2 score

Apostolakis … Lip. Chest 2013;144(5):1555-63

Acronym	**Definitions**	**Points**
S	**S**ex (female)	1
A	**A**ge (less than 60 years)	1
M e	**Me**dical history*	1
T	**T**reatment (interacting Rx eg. amiodarone for rhythm control)	1
T	**T**obacco use (within 2 years)	2
R	**R**ace (non Caucasian)	2
	Maximum points	8

*2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary disease, hepatic or renal disease.

'Using a mean TTR of approximately 0.65 as a cut off, the score could aid decision making by identifying those AF patients that would do well on VKA (SAMe-TT_2R_2 score=0-1), or conversely, those (ie. SAMe-TT_2R_2 score ≥2) who at risk of suboptimal anticoagulation control.'

Validation of the SAMe-TT_2R_2 score in a nationwide population of nonvalvular AF patients on VKAs

Ruiz-Ortiz et al Thromb Haemostat 2015; http://dx.doi.org/10.1160/TH15-02-0169

1,056 patients, mean age 73.6 ± 9.8 years, 42% female.

	SAMe-TT_2R_2 score					
	0−1 (n=613)	≥2 (n=443)	p-value	0−2 (n=929)	≥3 (n=127)	p-value
TTR	65.6%±26.2%	61.3%±25.3%	<0.005	64.3%±26%	60%±24.5%	<0.05
Proportion of INR in range	61.6%±24.9%	57.2%±24.6%	<0.01	60.7%±25.1%	56.3%±24.5%	<0.05
INR variability	0.20±0.26	0.22±0.24	<0.001	0.21±0.25	0.23±0.26	<0.01
Time above range	15.7%±20.1%	18.7%±22.1%	<0.05	15.9%±19.8%	19.8%±22.4%	<0.05
Patients with any INR >3 (n=725)	61.9%	77.9%	<0.001	66.2%	86.6%	<0.01
Time above INR >4	1.9%±6.3%	2.8%±7.4%	<0.05	2.0%±6.8%	3.2%±7.2%	<0.05
Patients with any INR >4 (n=368)	26.9%	45.1%	<0.001	31.12%	62.9%	<0.01

- Discriminated good anticoagulation control (TTR ≥65 %) with a C-statistic of 0.57 (95%CI 0.53–0.60, p<0.0005)
- Odds ratio of TTR< 65% if score was ≥ 2 was 1.64 (95 %CI 1.33–1.95, p<0.001)

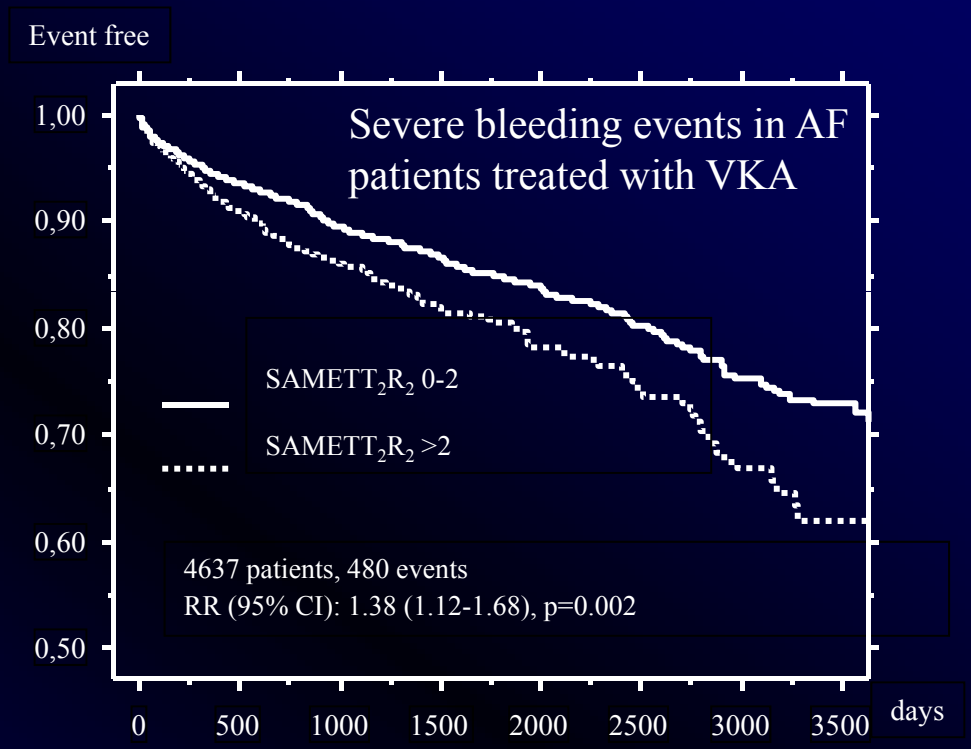
Relationship of the SAME-TT_2R_2 score to labile INR, stroke/thromboembolism, clinically relevant bleeding and mortality, in anticoagulated patients with AF

Lip et al, Chest 2014;146(3):719-26.

Amongst 'real world' AF patients on VKA (n=4637), the SAME-TT_2R_2 score was….

- Predictive of 'labile INR'
- Predictive of stroke/TE, severe bleeding, major BARC bleeding and death (c-statistics approximately 0.58), whilst on VKA

SAME-TT_2R_2 was non-predictive for non-VKA treated patients



In patients treated with a VKA, a higher mean SAME-TT_2R_2 score was also found for patients who developed stroke/TE during followup (p<0.0001), severe bleeding (p<0.0001), major BARC bleeding (p<0.0001) and death (p=0.001) .

Relation of the SAMe-TT_2R_2 score to quality of anticoagulation control and thromboembolic events in AF: SPORTIF

Proietti … Lip. Int J Cardiol 2016; 216: 168–172

N=3665 on warfarin; median TTR 86.5%

Lower proportions of patients with SAMe-TT_2R2_2 >2 with a TTR >65% and TTR >70% (p = 0.014 and p = 0.011, respectively), compared to those with SAMe-TT_2R2_2 0–2

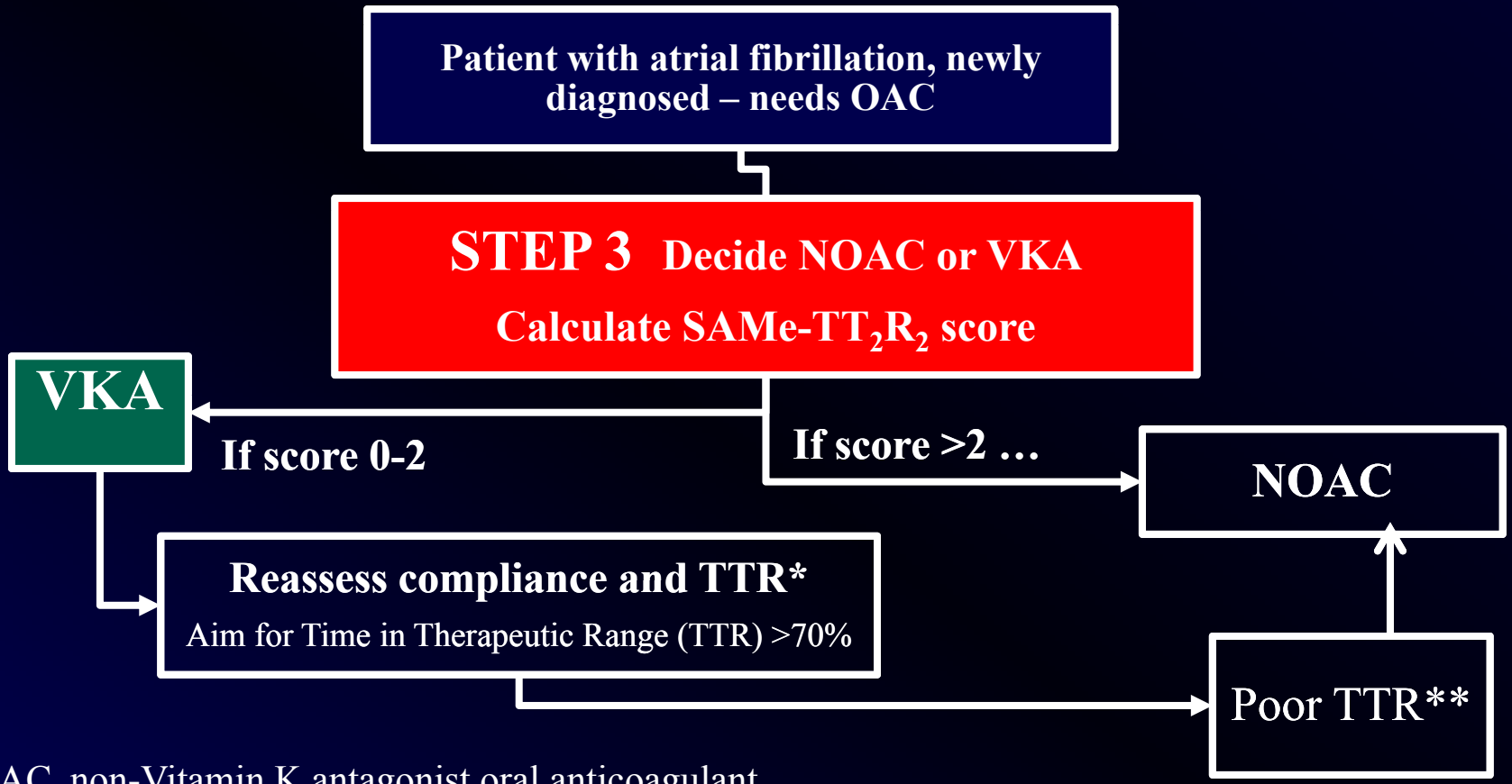
	TTR >65%			**TTR >70%**		
	OR	95%CI	P	OR	95%CI	P
SAMe-TT_2R_2 [per point]	0.91	0.86-0.96	0.001	0.91	0.86-0.96	0.001
SAMe-TT_2R_2 >2	0.81	0.69-0.96	0.014	0.81	0.68-0.95	0.011

On Cox multivariate regression analysis, adjusted for type of AF and previous VKA use, etc

- SAMe-TT_2R2_2 score as a continuous variable was significantly associated with the composite outcome (hazard ratio [HR]: 1.14, 95% CI: 1.04–1.26; p = 0.005).
- SAMe-TT_2R2_2 score category significantly associated with the composite outcome (HR: 1.37, 95% CI: 1.05–1.78; p = 0.020).

NOAC or VKA at initial consultation? Not guesswork!

Lip & Lane, JAMA 2015;313(19):1950-1962.



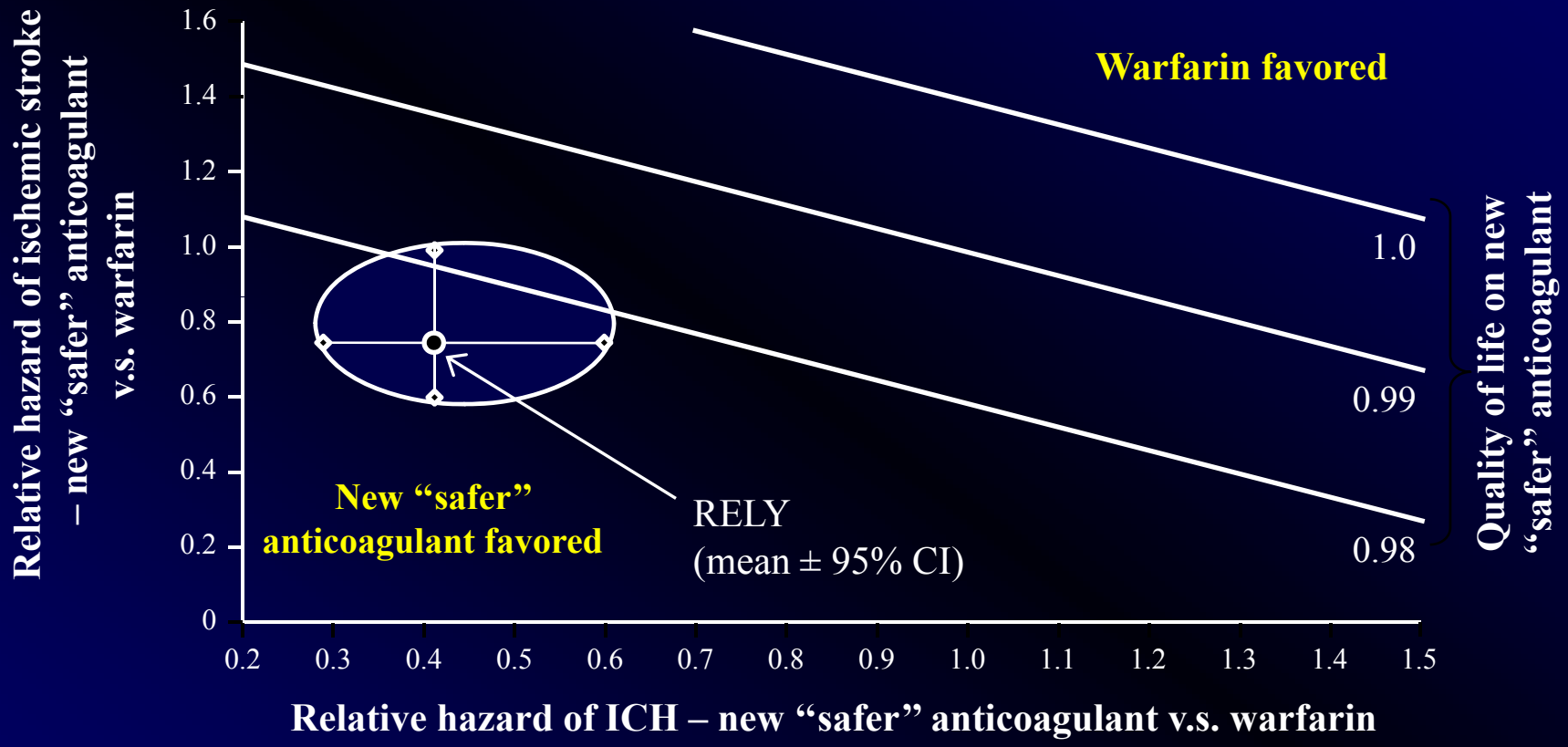
NOAC, non-Vitamin K antagonist oral anticoagulant

*When calculating TTR, use a validated method (eg. Rosendaal method for computer-assisted dosing) or proportion of tests in range for manual dosing. Exclude measurements taken during the first 6 weeks of treatment and calculate TTR over a maintenance period of at least 6 months.

**Reassess if poor anticoagulation control shown by any of the following: 2 INR values >5 or 1 INR value >8 within the past 6 months; 2 INR values <2.0 within the past 6 months; TTR <65%.

Moving the Tipping Point The Decision to Anticoagulate Patients With Atrial Fibrillation

Eckman, et al Circ Cardiovasc Qual Outcomes 2011 Jan 1;4(1):14-21.



With the addition of a new, "safer" agent as another option for anticoagulation, the "tipping point" above which the risk and outcomes of ischemic stroke outweigh the risk and outcomes of major hemorrhage shifts to the left.

Anticoagulation with NOAC is preferred at annual stroke rates above 0.9% /year [for warfarin the threshold is 1.7%/year]

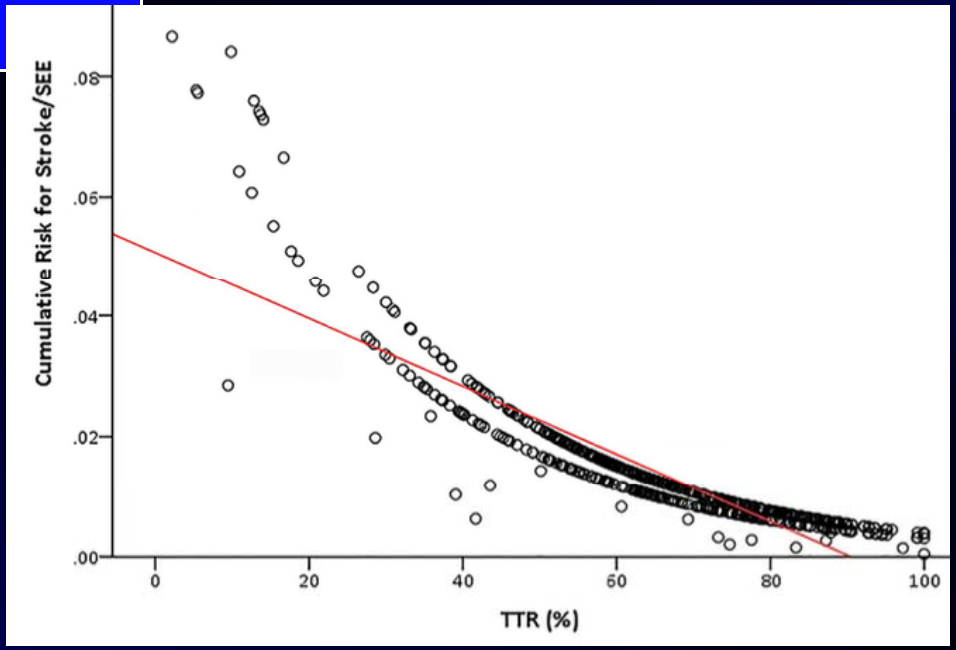
Major Outcomes in Atrial Fibrillation Patients with One Risk Factor: Impact of Time in Therapeutic Range [SPORTIF]

Proietti and Lip Am J Med 2015; DOI 10.1016/j.amjmed.2016.03.024

Per 100 pt/yrs	Stroke/SE	All cause death	Composite
Hypertension	0.9	1.4	2.1
Diabetes	1.4	0	1.4
Vascular disease	0.5	1.6	2.0
CHF	1.1	3.7	4.4

Warfarin patients (n=1097) from SPORTIF trial

Scatterplot and Regression Line between TTR and Cumulative Risk for Stroke/SE

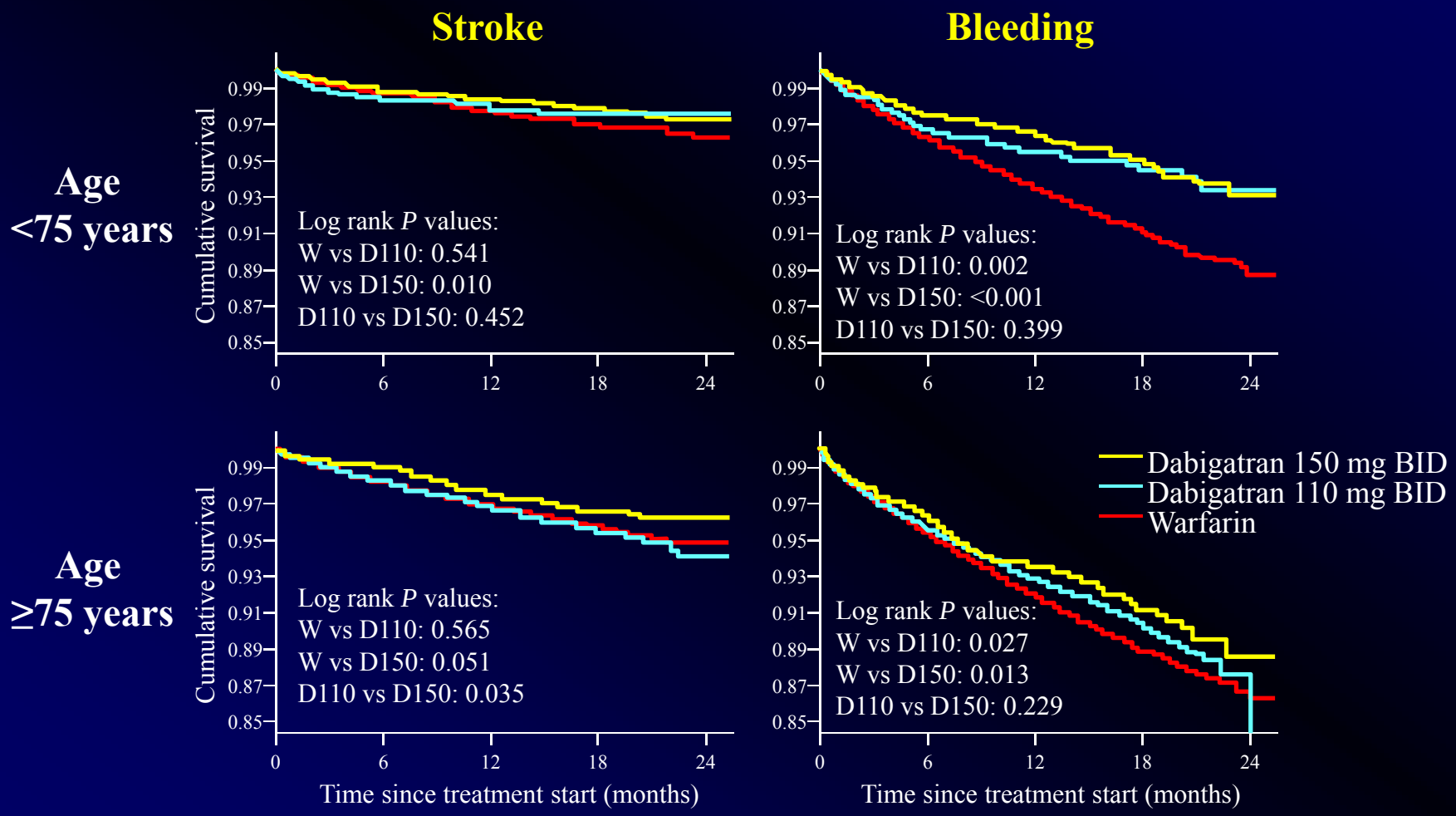


Cox regression analysis in patients treated with warfarin only found TTR to be inversely associated with stroke/SE (p=0.034) and all-cause death (p=0.015)

Dabigatran use in elderly patients with AF

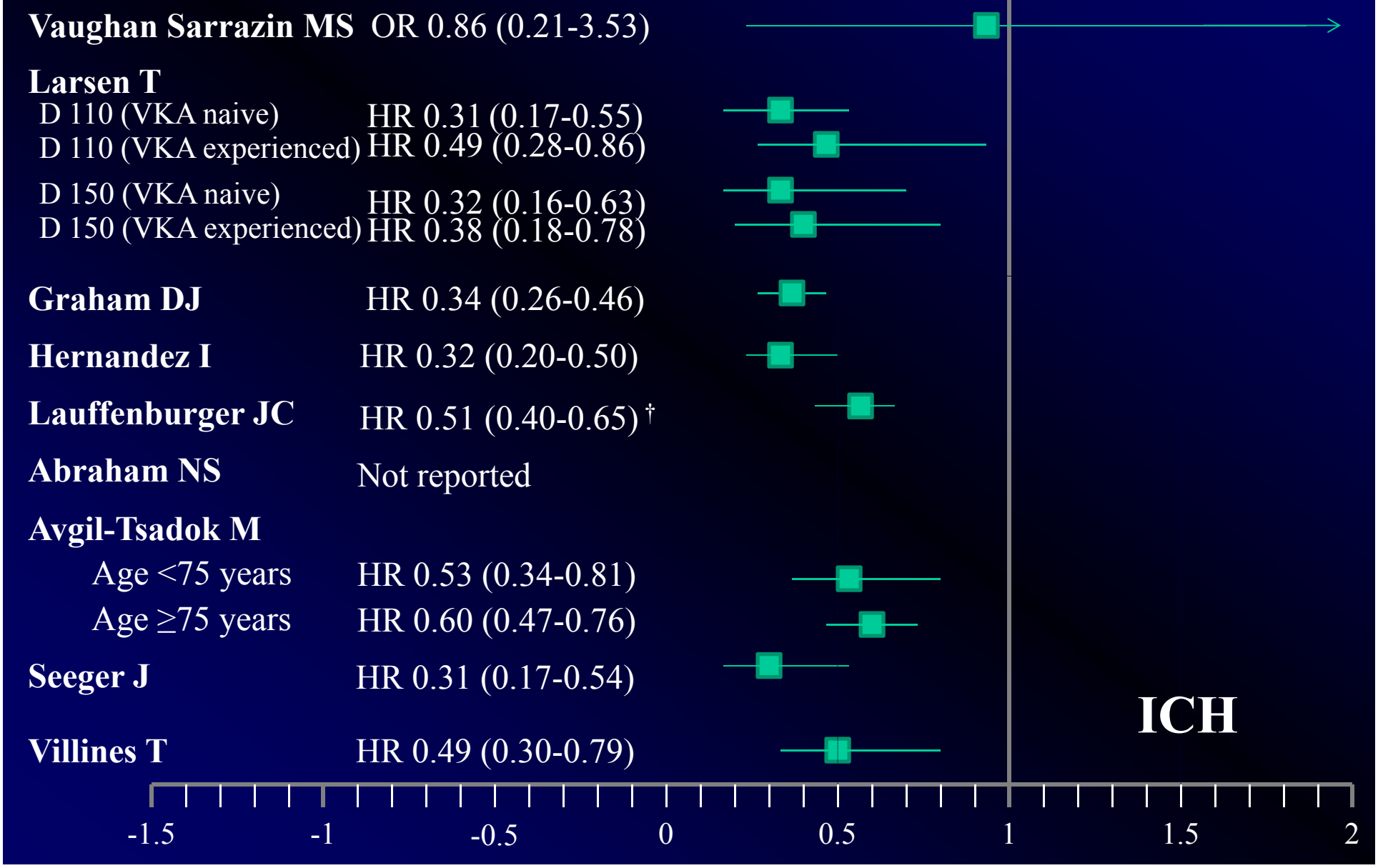
Avgil-Tsadok et al Thromb Haemostat 2015; http://dx.doi.org/10.1160/TH15-03-0247

15,918 dabigatran users vs 47,192 matched warfarin users (67.3% elderly, age ≥75 years)



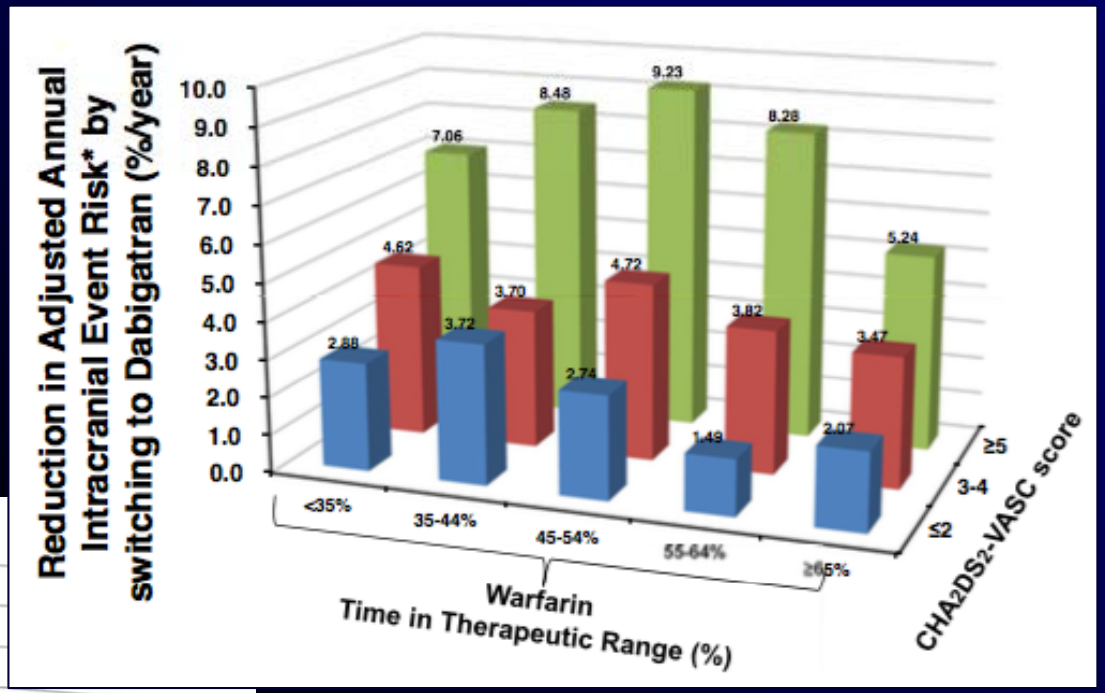
Dabigatran in 'real-world' clinical practice for AF

Potpara T. Thromb Haemostat 2015 http://dx.doi.org/10.1160/TH15-10-0825

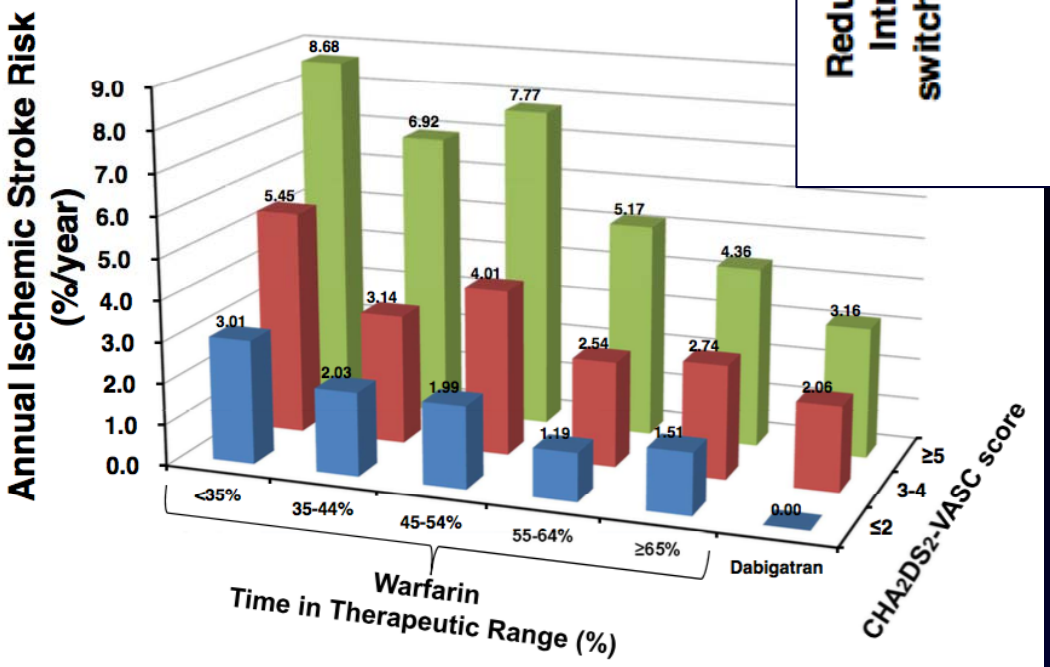


Net Clinical Benefit of NOAC over Warfarin in Patients with AF Stratified by CHA_2DS_2-VASc Score and TTR

Chan .. Lip et al Can J Cardiol 2016
doi: 10.1016/j.cjca.2016.01.016.



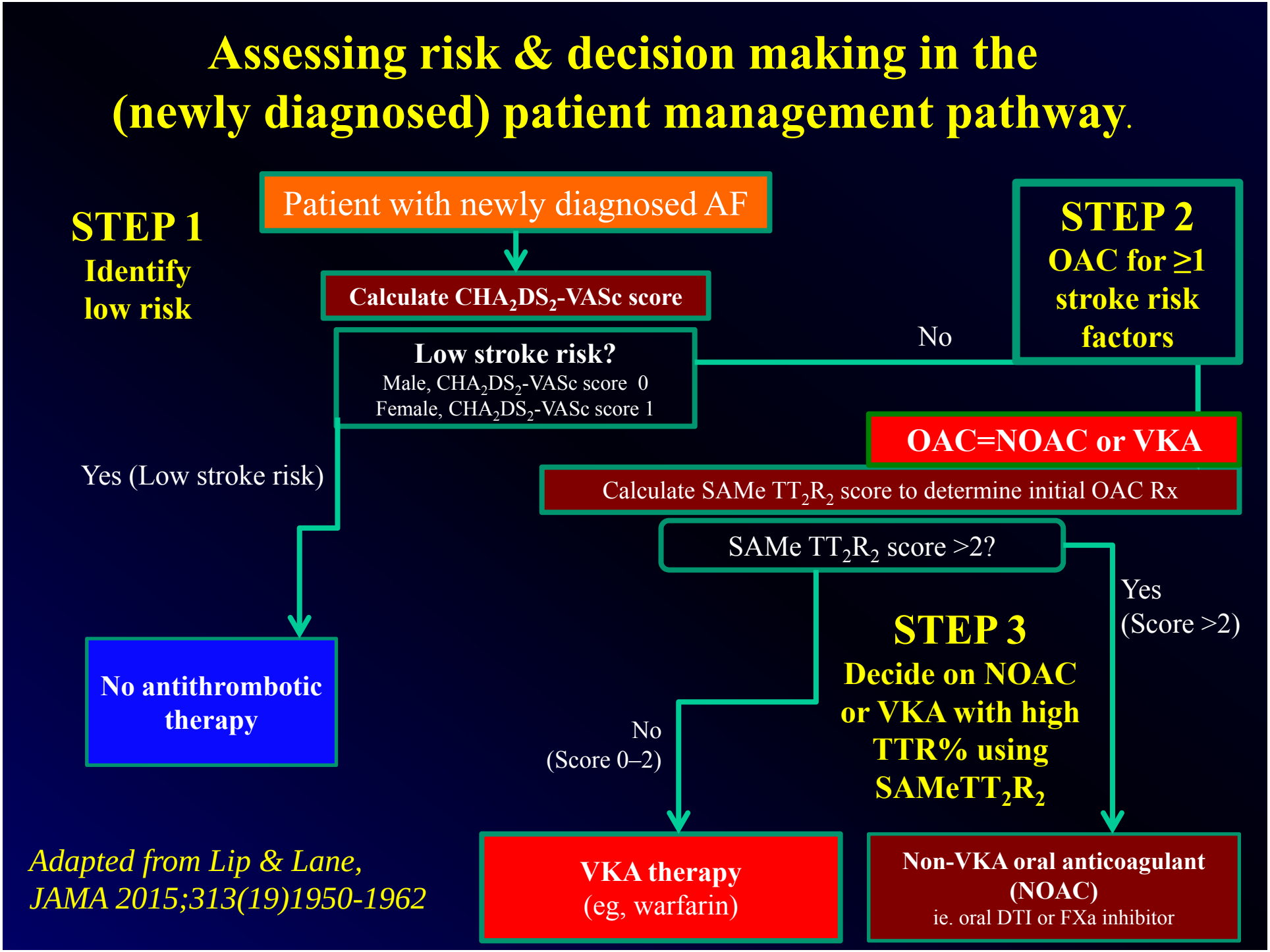
Net clinical benefit of switching warfarin at different time in therapeutic range (TTR) to dabigatran across different strata of CHA_2DS_2VASc score.



Relation between CHA_2DS_2VASc score and warfarin at different time in therapeutic range (TTR) and dabigatran, and the annual risk of ischemic stroke

The best NCB for switching warfarin to NOAC was found in those with both high CHA_2DS_2VASc score and poor TTR.

Assessing risk & decision making in the (newly diagnosed) patient management pathway.



Adapted from Lip & Lane, JAMA 2015;313(19)1950-1962

iTunes Preview

HKU AF CAL

By Hin Wai Lui

Open iTunes to buy and download apps.

View in iTunes

This app is designed for both iPhone and iPad

Description

HKU AF CAL is calculates for physicians and patients the
the following calculators:
-Percent time in therapeutic INR range
-SAMe-TT_2R_2
-HAS-BLED
-CHA_2DS_2-VASc
-Cockcroft-Gault

This Application is jointly developed by The University o

HKU AF CAL Support

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Advisors:, Azhar Ahmad, M.D. (Boehringer Ingelheim Pharma), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim Pharma), Susanne Hess, M.D. (Bayer Healthcare Pharmaceuticals), Markus Müller, M.D., Ph.D. (Pfizer Pharma), Felix Münzel, Ph.D. (Daiichi-Sankyo Europe), Markus Schwertfeger, M.D. (Daiichi-Sankyo Europe), Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)

Document reviewers:, Gregory Y.H. Lip, (Reviewer Coordinator; UK), Chern-En Chiang, (Taiwan), Jonathan Piccini, (USA), Tatjana Potpara, (Serbia), Laurent Fauchier, (France), Deirdre Lane, (UK), Alvaro Avezum, (Brazil), Torben Bjerregaard Larsen, (Denmark), Guiseppe Boriani, (Italy), Vanessa Roldan-Schilling, (Spain), Bulent Gorenek, (Turkey), and Irene Savelieva, (UK, on behalf of EP-Europace)

Things to consider when starting/choosing a NOAC … think ABCDE

Lip et al Nat Rev Dis Primers. 2016 Mar 31;2:16016. doi: 10.1038/nrdp.2016.16.

A	Abnormally low weight (dose reduction may be needed with some agents)
B	Bleeding risk, esp. gastrointestinal
C	Creatinine clearance (as a measure of renal function)
D	Drug interactions (eg. reduce dose of verapamil with dabigatran)
E	Elderly age (dose reduction may be needed)

Professor Martin Green lecture:

Stroke prevention in atrial fibrillation: Past, present and future

Simplicity is best!

CHA_2DS_2-VASc is simple and best at initial identification of "truly low risk" patients who do not need any antithrombotic therapy

– All others with ≥1 stroke risk factors can be offered effective stroke prevention, which is OAC

HAS-BLED to 'flag up' patients potentially at risk, and to address potentially correctable risk factors for bleeding.

– A high HAS-BLED score should not be used to withhold OAC

With VKAs, we must aim for good quality anticoagulation control, with TTR >70%

The SAMe-TT_2R_2 score helps decision making between NOAC and VKA

NOACs offer relative efficacy, safety and convenience compared to VKAs, but *fit the drug to the patient (and vice versa).*

Think ABCDE when considering NOAC type/dose