Révolution dans la prise en charge du risque thromboembolique de la FA

ESC 2012 : un nouveau regard

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APPAC

APPAC 6 juin 2013

Relations avec l'industrie

- **Maxime GUENOUN 2011 - 2012:**

Consulting scientifique, Conférences, Invitations:

- Astra-Zeneca, Biopharma, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Eli-Lilly,
- Merck-Serono, MSD-Schering, Novartis, Pfizer, Pierre Fabre, Sanofi-Aventis, Servier, Bayer Healthcare, Ipsen,
- Medtronic, Sorin Group, Saint Jude Médical, Boston Scientific.

New /Modified Recommendations

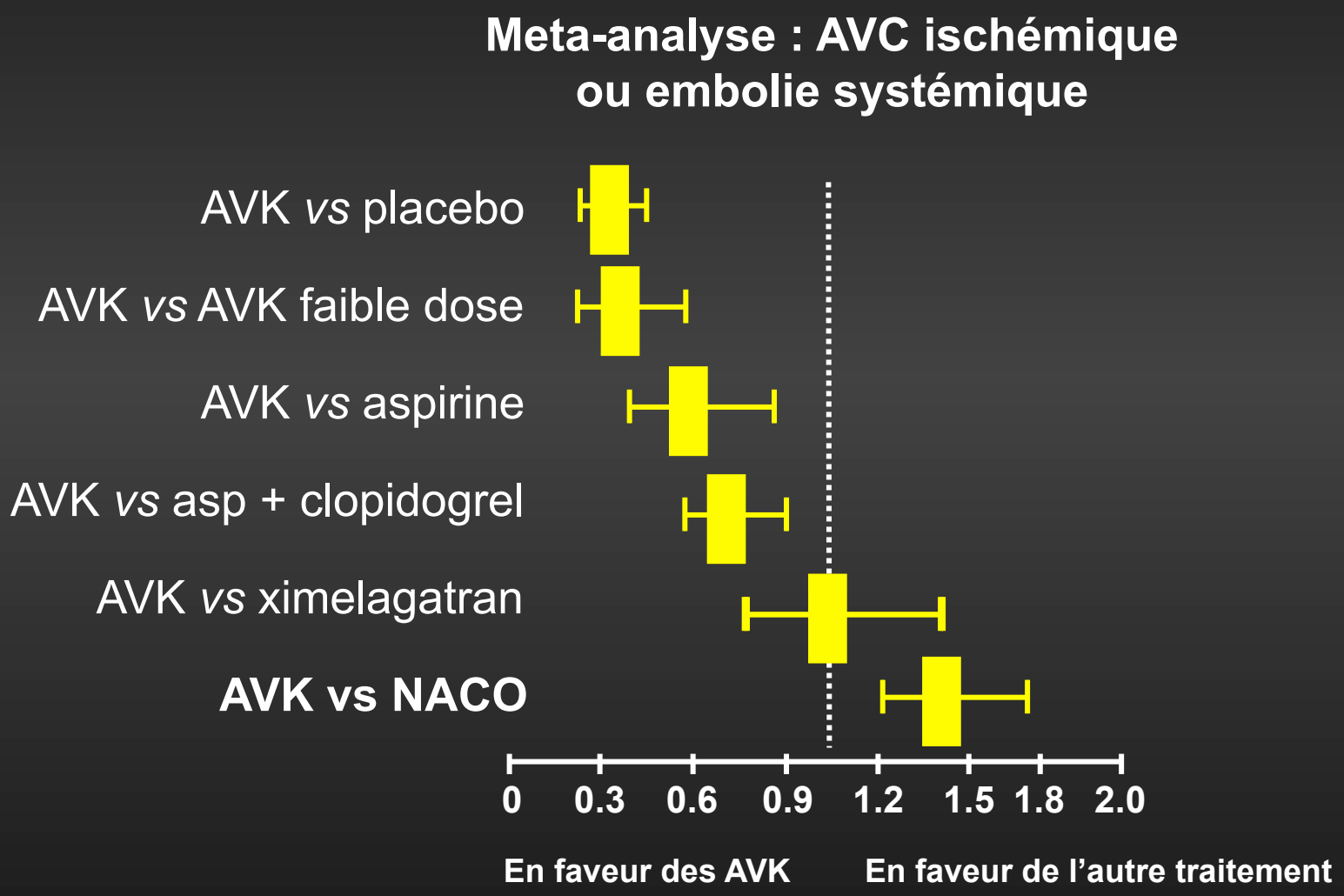
Topic	A	B	C	I	IIa	IIb	III
Anticoagulation risk stratification	6	7		6	7		
Anticoagulation	2	5	1	3	4		1
Left atrial appendage occlusion		1	1			2	
Pharmacological cardioversion	1	2		1	2		
Oral antiarrhythmic therapy	1	2		1		1	1
Left atrial catheter ablation	2	3		1	4		
Total n (%)	12 (35%)	20 (59%)	2 (9%)	12 (35%)	17 (50%)	3 (9%)	2 (9%)

Anticoagulation - General

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A

ESC Update on the Management of AF: European Heart Journal/EP- Europace 2012

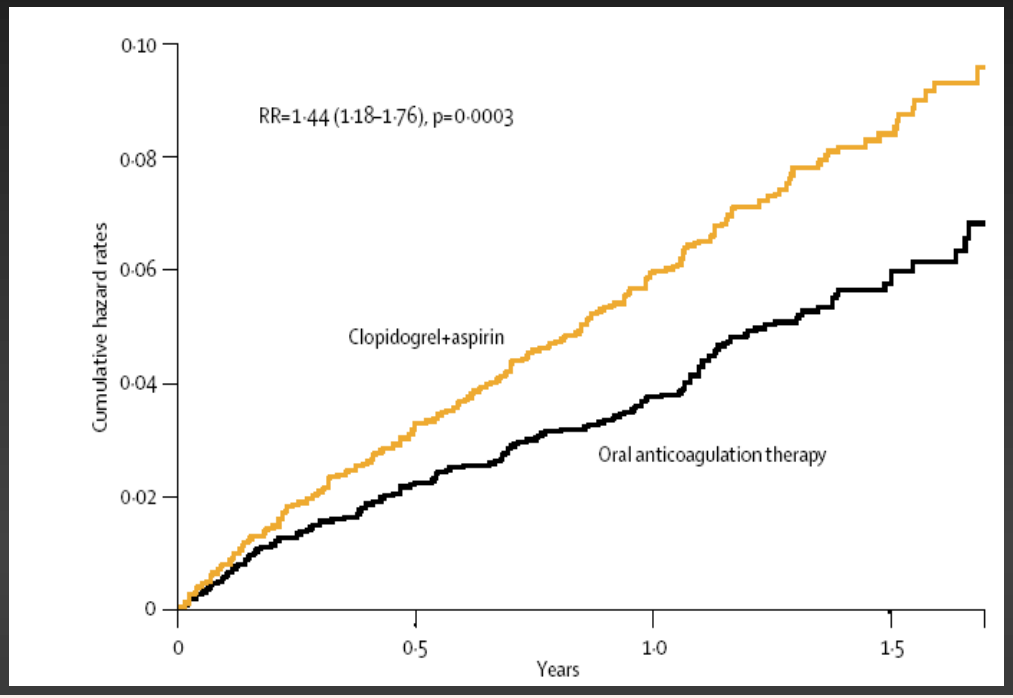
Prévention des AVC dans la FA



NACO : Nouveaux AntiCoagulants Oraux

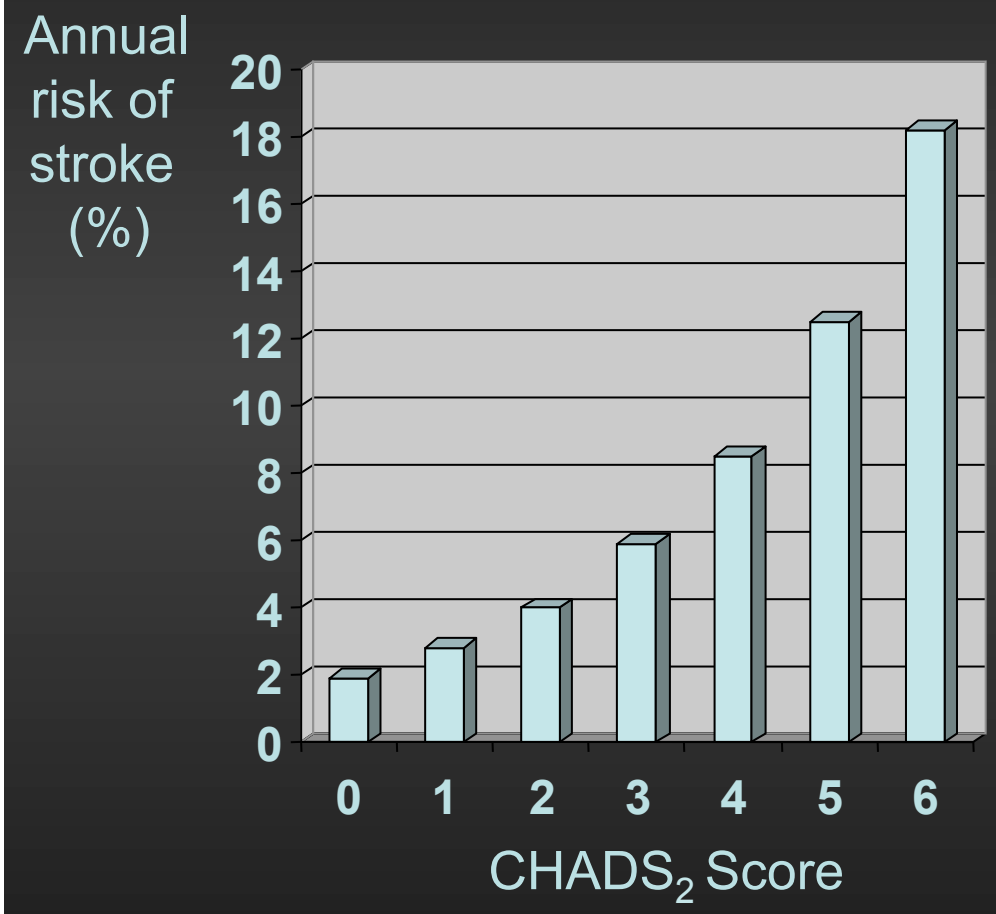
ACTIVE W, *Lancet 2006*

Primary outcome :
stroke, non-CNS systemic embolus, MI, or vascular death.



	Clopidogrel+aspirin		Oral anticoagulation		Clopidogrel+aspirin vs oral anticoagulatio	
	Number	Risk (% per year)	Number	Risk (% per year)	RR (95% CI)	p
Haemorrhage						
Major (includes severe and fatal)	101	2·42	93	2·21	1·10 (0·83–1·45)	0·53
Severe	71	1·70	66	1·57	1·09 (0·78–1·52)	0·62
Fatal	7	0·17	11	0·26	0·64 (0·25–1·66)	0·36
Minor	568	13·58	481	11·45	1·23 (1·09–1·39)	0·0009
Total	644	15·40	555	13·21	1·21 (1·08–1·35)	0·001
Net benefit						
Primary outcome and major bleed	316	7·56	229	5·45	1·41 (1·19–1·67)	<0·0001
Primary outcome, major bleed, and death	348	8·32	271	6·45	1·31 (1·12–1·54)	0·0008

AF : $CHADS_2$ Score

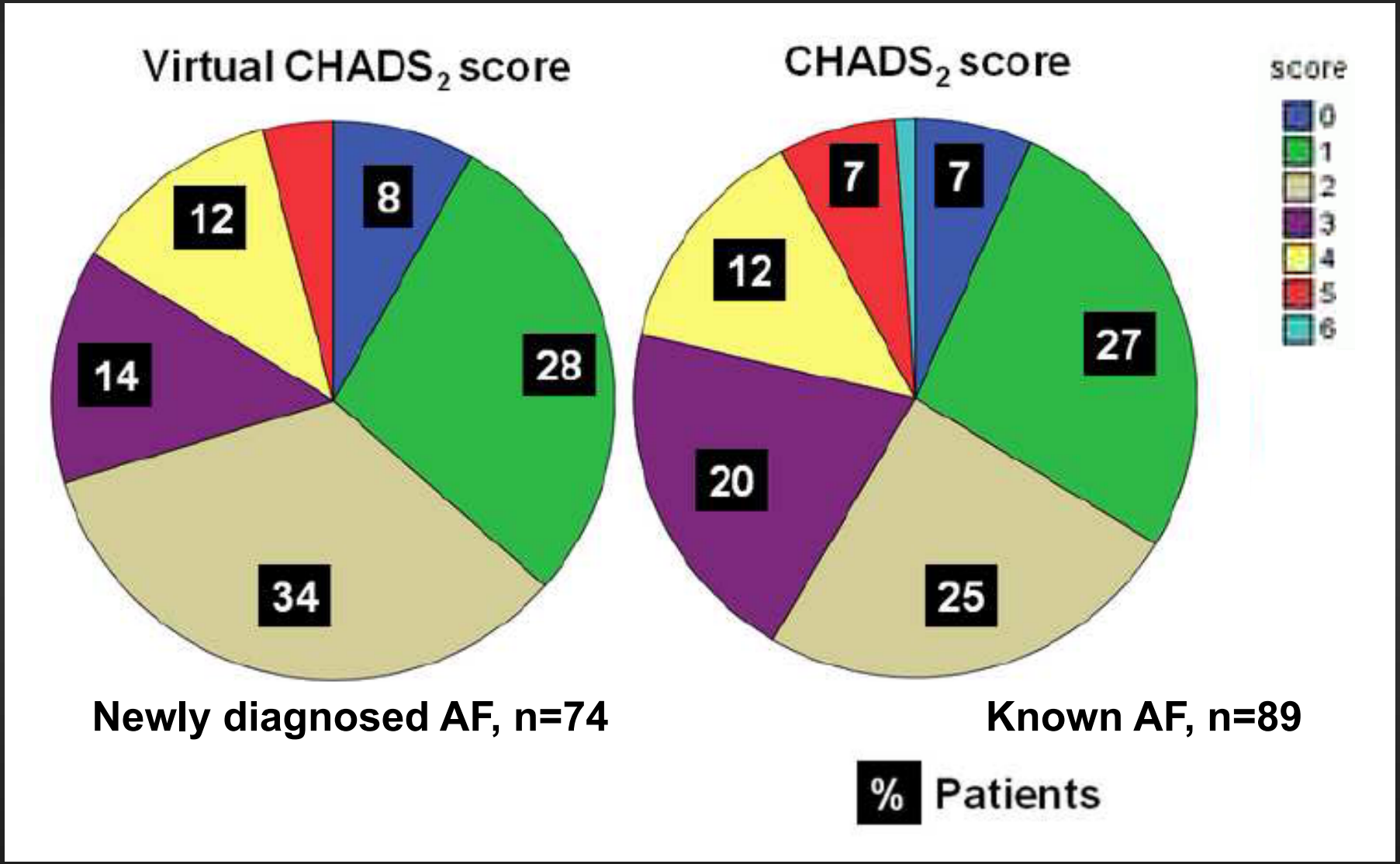


- CHF +1
- Hypertension +1
- Age >75 +1
- Diabetes +1
- Stroke +2

Score $CHADS_2$ max = 6

Adapted from Gage et al, *JAMA 2001*

Patients with Ischemic Stroke (n=1120) and AF



Pisters R, et al. *Europace 2010*

The CHA_2DS_2VASc score in non-valvular AF

A	
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

Lip GYH, Nieuwlaat R, Pisters R, et al. *Chest 2010*

Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with AF

***Olesen, Lip et al BMJ* 2011**

Scale†	Event rates per 100 person-y			At 1 y
	Low risk (score 0)	Intermediate risk (score 1)	High risk (score > 1)	C-statistic (95% CI)‡
$CHADS_2$	1.7	4.8	12	0.72 (0.69 to 0.75)
CHA_2DS_2-VASc	0.78	2.0	8.8	0.85 (0.83 to 0.87)
				At 5 y
$CHADS_2$	1.3	3.7	8.3	0.80 (0.78 to 0.81)
CHA_2DS_2-VASc	0.69	1.5	6.0	0.88 (0.87 to 0.89)
				At 10 y
$CHADS_2$	1.2	3.6	8.0	0.81 (0.80 to 0.83)
CHA_2DS_2-VASc	0.66	1.5	5.7	0.89 (0.88 to 0.90)

†$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥ 75 y, Diabetes mellitus, and previous thromboembolism (double points); CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥ 75 y (double points), Diabetes mellitus, previous thromboembolism (double points), Vascular disease, Age 65 to 74 y, and female Sex.

‡Based on Cox regression models using 3 risk groups and with covariates analyzed as categorical variables.

CHA2DS2-VASc adds when CHADS2 = 0–1
A nationwide cohort study

	$CHADS_2$ score = 0 n=19,444	$CHADS_2$ score = 1 n=28,132
Age, mean (SD)	58.8 (11.9)	76.8 (11.6)
Congestive heart failure	0	949 (3.4)
Hypertension	0	8,081 (28.7)
Age ≥75 years	0	18,183 (64.6)
Diabetes mellitus	0	919 (3.3)
Stroke (previous)	0	0
Vascular disease	1,592 (8.2)	4,199 (14.9)
Age 65–74 years	7,526 (38.7)	5,517 (19.6)
Sex category (female)	7,258 (37.3)	14,759 (52.5)
Antiplatelet treatment		
Aspirin	3,322 (17.1)	8,937 (31.8)
Clopidogrel or persantine	332 (1.7)	1,040 (3.7)
CHA_2DS_2-VASc score		
0	7,536 (38.8)	0
1	7,739 (39.8)	2,323 (8.3)
2	3,870 (19.9)	10,440 (37.1)
3	299 (1.5)	13,389 (49.4)
4	0	1,480 (5.3)

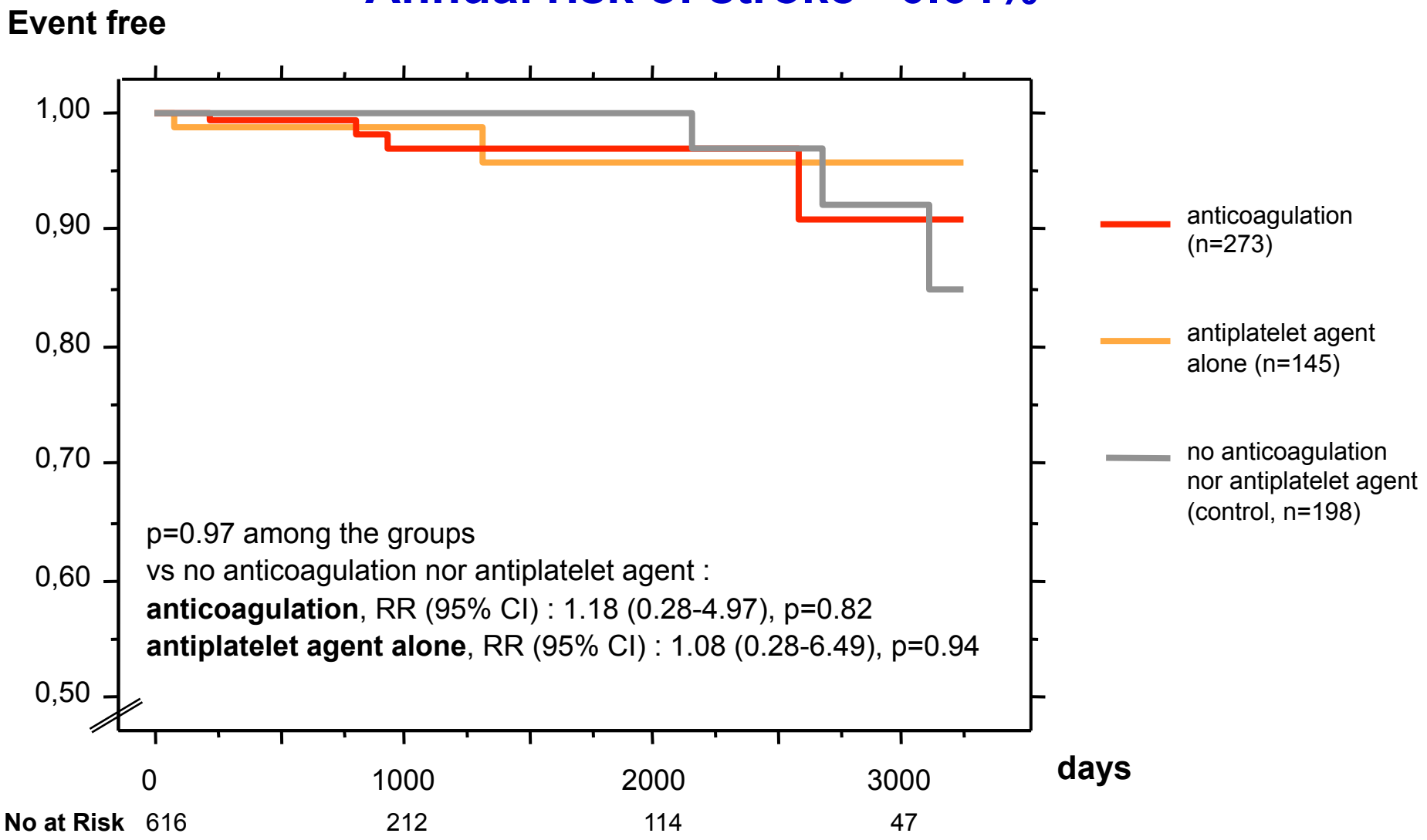
	1 year follow-up
	Stroke rate (95%CI)
$CHADS_2$ score 0–1	3.49 (3.31–3.68)
CHA_2DS_2-VASc = 0	0.84 (0.65–1.08)
CHA_2DS_2-VASc = 1	1.79 (1.53–2.09)
CHA_2DS_2-VASc = 2	3.67 (3.34–4.03)
CHA_2DS_2-VASc = 3	5.75 (5.33–6.21)
CHA_2DS_2-VASc = 4	8.18 (6.68–10.02)
$CHADS_2$ score = 0	1.59 (1.41–1.79)
CHA_2DS_2-VASc = 0	0.84 (0.65–1.08)
CHA_2DS_2-VASc = 1	1.75 (1.46–2.09)
CHA_2DS_2-VASc = 2	2.69 (2.19–3.31)
CHA_2DS_2-VASc = 3	3.20 (1.60–6.40)
$CHADS_2$ score = 1	4.92 (4.65–5.22)
CHA_2DS_2-VASc = 1	1.93 (1.42–2.64)
CHA_2DS_2-VASc = 2	4.05 (3.65–4.50)
CHA_2DS_2-VASc = 3	5.81 (5.38–6.27)
CHA_2DS_2-VASc = 4	8.18 (6.68–10.02)

Olesen J. et al. *Thromb Haemost. 2012*

Stroke/TE event in AF with CHA_2DS_2VASc score =0

616 patients, 862±1122 days FU, 10 events

Annual risk of stroke =0.64%

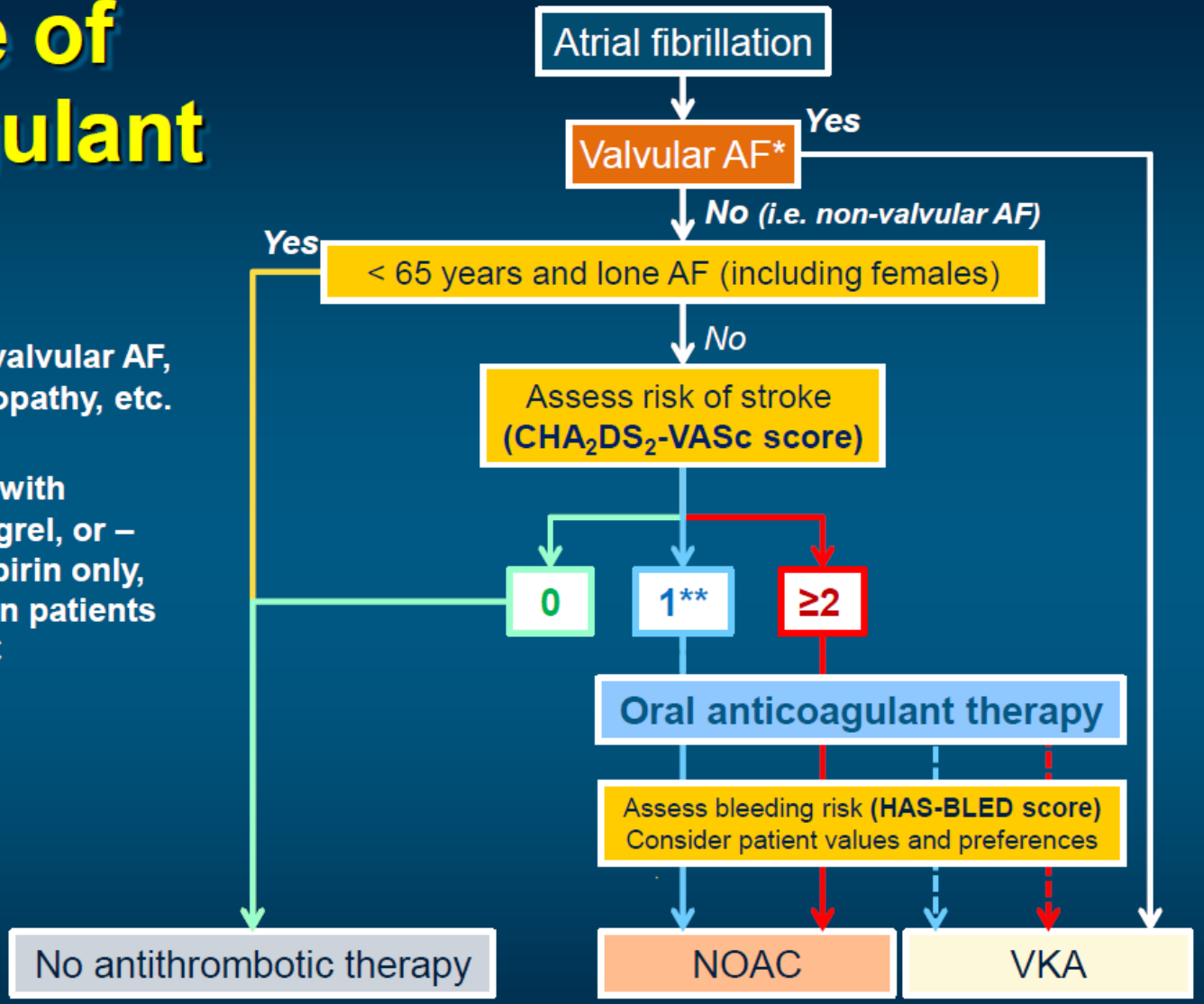


Taillandier S, et al. *J Cardiovasc Electrophysiol 2012 (in press)*

Choice of Anticoagulant

* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC



European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

The CHA_2DS_2-VASc risk factors
The Loire Valley Atrial Fibrillation Project

- 6,438 patients with non-valvular AF, 2000-2010
- Risk of stroke and thromboembolism in patients aged <65 years

	Multivariate Hazard ratio (95% CI)
Heart failure	1.95 (1.04-3.66)
Hypertension	0.90 (0.49-1.66)
Diabetes	1.76 (0.86-3.59)
Previous stroke	5.66 (2.91-11.02)
Vascular disease	2.19 (1.22-3.92)
Female gender	0.70 (0.34-1.43)

Female gender as a risk factor does vary in different studies…

Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. *Chest 2011*

L'évaluation du risque de saignement

Scoring system	% Annual bleeding risk		
	Low bleed risk	**Medium bleed risk**	**High bleed risk**
OBRI (outpatient bleeding risk index)[34] *One point each*: age ≥65, history of stroke, history of GI bleed *One point (max) for any of the following*: recent MI, Hct <30%, Cr >1.5 mg/dL, diabetes	Score = 0; 3%	Score = 1–2; 8%	Score = 3–4; 30%
$HEMORR_2HAGES$[35] *One point each*: hepatic or renal disease, ethanol abuse, malignancy, older age (age >75 years), reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors, excessive fall risk, stroke *Two points*: rebleeding risk	Score = 0–1; ~2–2.5%	Score = 2–3; ~5–8%	Score = 4–11; >10%
Shireman *et al.*[33] $\text{Score} = 0.49(X)_{\text{Age 70+}} + 0.32(X)_{\text{Female}} + 0.58(X)_{\text{Remote bleed}} + 0.62(X)_{\text{Recent bleed}} + 0.71(X)_{\text{Alcohol/drug abuse}} + 0.27(X)_{\text{Diabetes}} + 0.86(X)_{\text{Anaemia}} + 0.32(X)_{\text{Antiplatelet}}$ $X = 1$ when the specific characteristic is present and 0 if absent	Score ≤ 1.07; 1%	1.07 < score < 2.19; 2%	Score ≥ 2.19; 5%
HAS-BLED[36] *One point each*: hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, labile INRs, elderly age >65, drugs, alcohol	Score = 1–2; ~1–2%	Score = 3–4; ~4–9%	Score = 5–9; >12%

Yang F et al., Europace 2011

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

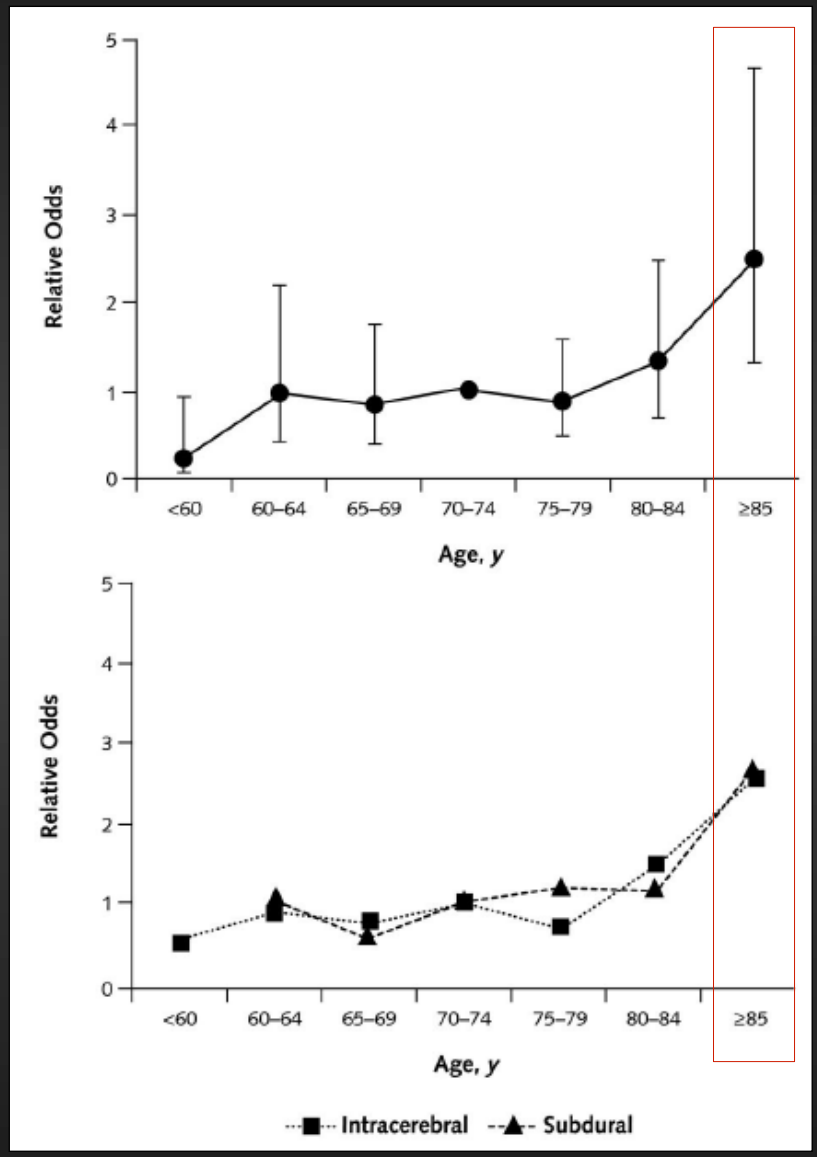
Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

AF - ESC Guidelines, *EHJ 2010*

Age et hémorragie intracranienne

Hémorragies
intra-crâniennes

Cas-témoins
175 pts H^{ie} intra-crânienne
vs 1020 témoins

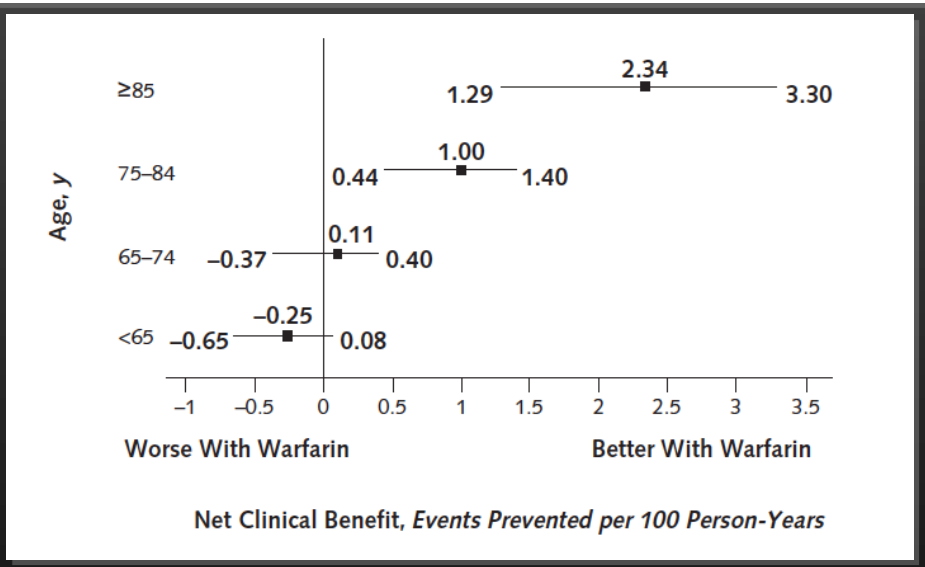


Fang MC et al., Ann Intern Med 2004

Net Clinical Benefit of Warfarin in AF
ATRIA cohort, *Ann Int Med 2009*

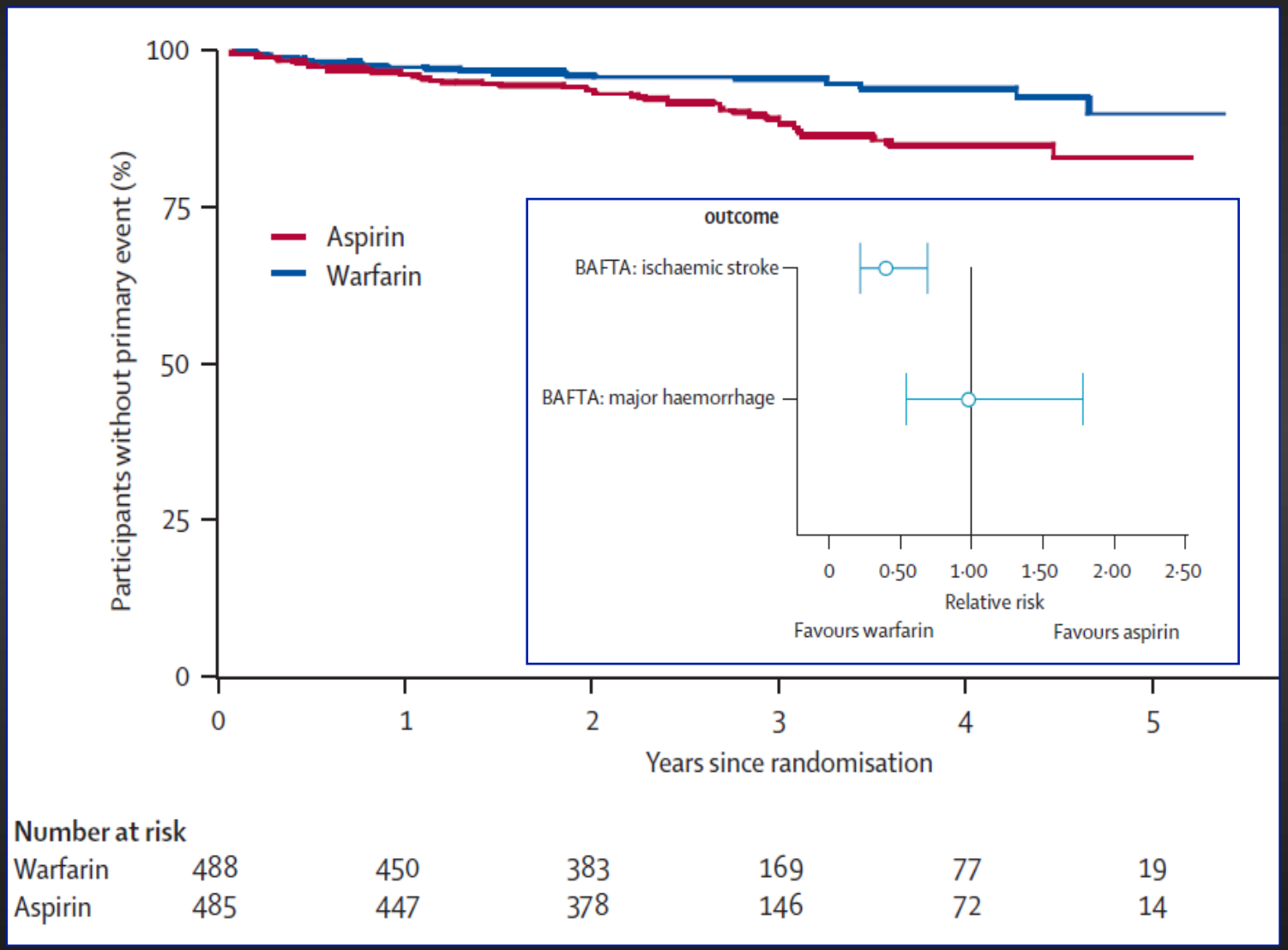
Table 3. Annual Net Clinical Benefit of Warfarin Therapy Overall and by Individual Risk Factors, Using Different Weights for ICH

Risk Factor	Net Clinical Benefit (95% CI)*		
	ICH Weight = 1.5 (Base Case)	ICH Weight = 1	ICH Weight = 2
All patients	0.68 (0.34 to 0.87)	0.80 (0.51 to 0.96)	0.56 (0.18 to 0.77)
Age			
<65 y	−0.25 (−0.65 to 0.08)	−0.15 (−0.48 to 0.14)	−0.35 (−0.81 to 0.05)
65–74 y	0.11 (−0.37 to 0.40)	0.27 (−0.16 to 0.55)	−0.05 (−0.58 to 0.27)
75–84 y	1.00 (0.44 to 1.40)	1.09 (0.59 to 1.44)	0.92 (0.29 to 1.34)
≥85 y	2.34 (1.29 to 3.30)	2.51 (1.62 to 3.37)	2.17 (0.93 to 3.18)



BAFTA : AF age≥75 - 1ary endpoint

Fatal or disabling stroke, intracranial haemorrhage, or arterial embolism.



Number at risk						
Warfarin	488	450	383	169	77	19
Aspirin	485	447	378	146	72	14

Lancet 2007

FA: Risque de saignement

- Un score HASBLED ≥3 témoigne d'un risque hémorragique plus élevé...
- ... mais ne constitue pas une contrindication au traitement anticoagulant
- Des précautions et un suivi régulier du patient sont alors nécessaires après l'initiation du traitement antithrombotique

Camm AJ et al, *Eur Heart J* 2010;31:2369-429

FA: Risque de saignement

2012 update of the ESC Guidelines for the management of AF

Recommendations	Class[a]	Level[b]
Recommendations for prevention of thromboembolism in non-valvular AF—bleeding		
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	A B
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B

Camm AJ et al, *Eur Heart J* 2012

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

Olesen, Lip et al. *Thromb Hemostat 2011*

Net clinical benefit = (ischaemic stroke rate with no treatment - ischaemic stroke rate on treatment) - 1.5(ICH rate on treatment - ICH rate with no treatment)

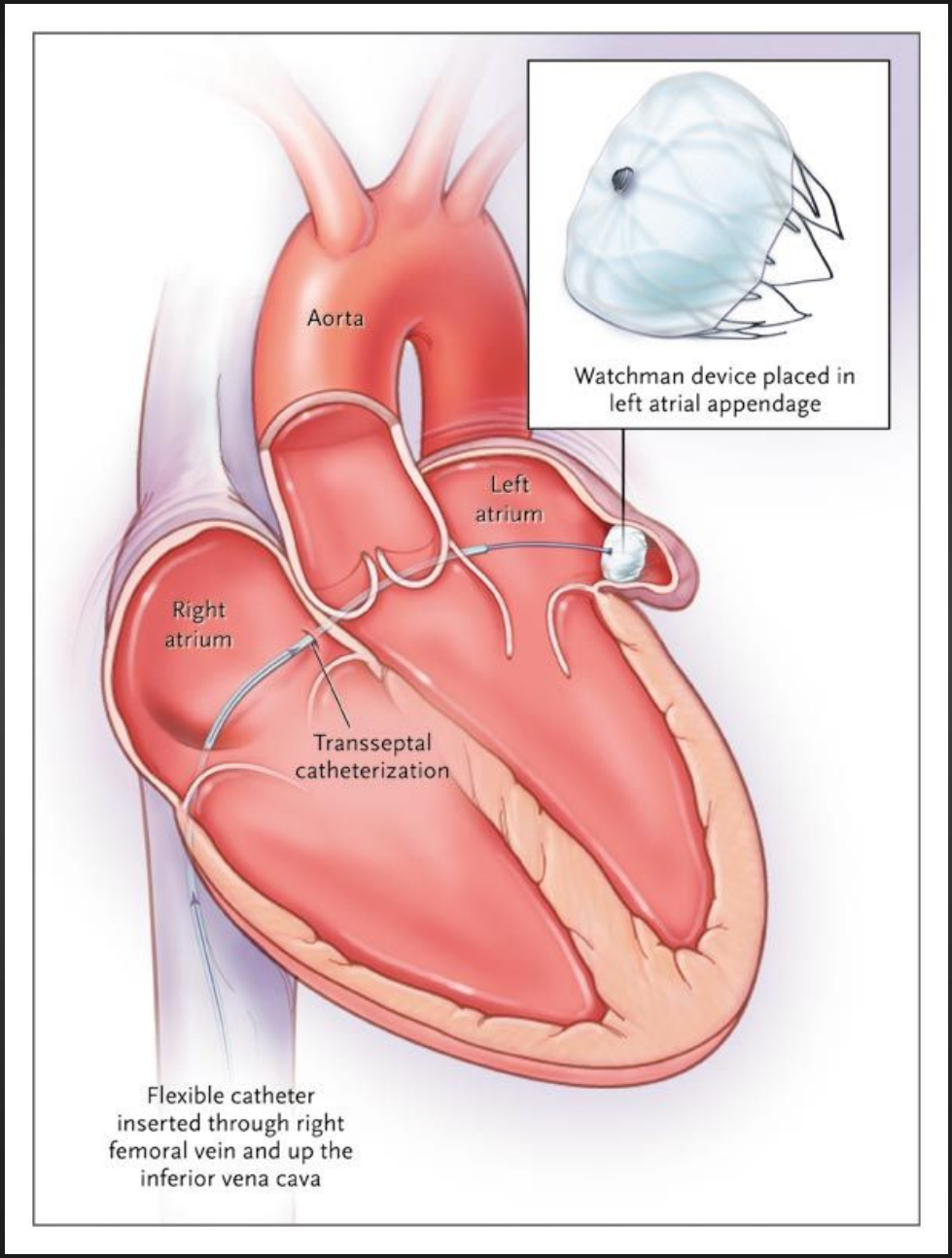
Net clinical benefit* (%, 95%CI) **VKA vs. no Rx**

		HAS-BLED ≤2	HAS-BLED ≥3
$CHADS_2$	Score 0	-0.02 (-0.09 to 0.06)	0.19 (-1.39 to 1.77)
	Score 1	0.84 (0.70 to 0.99)	0.56 (0.16 to 0.95)
	Score 2-6	1.95 (1.70 to 2.20)	2.68 (2.33 to 3.04)
CHA_2DS_2-VASc	Score 0	-0.11 (-0.20 to -0.03)	…
	Score 1	-0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)
	Score 2-9	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)

Negative net clinical benefit (ischaemic stroke vs. intracranial haemorrhage) with VKA only in patients with a CHA_2DS_2-VASc score of 0, reflecting their 'truly low risk' status.

WATCHMAN®
device

Atritech, Inc
Plymouth, MN, USA

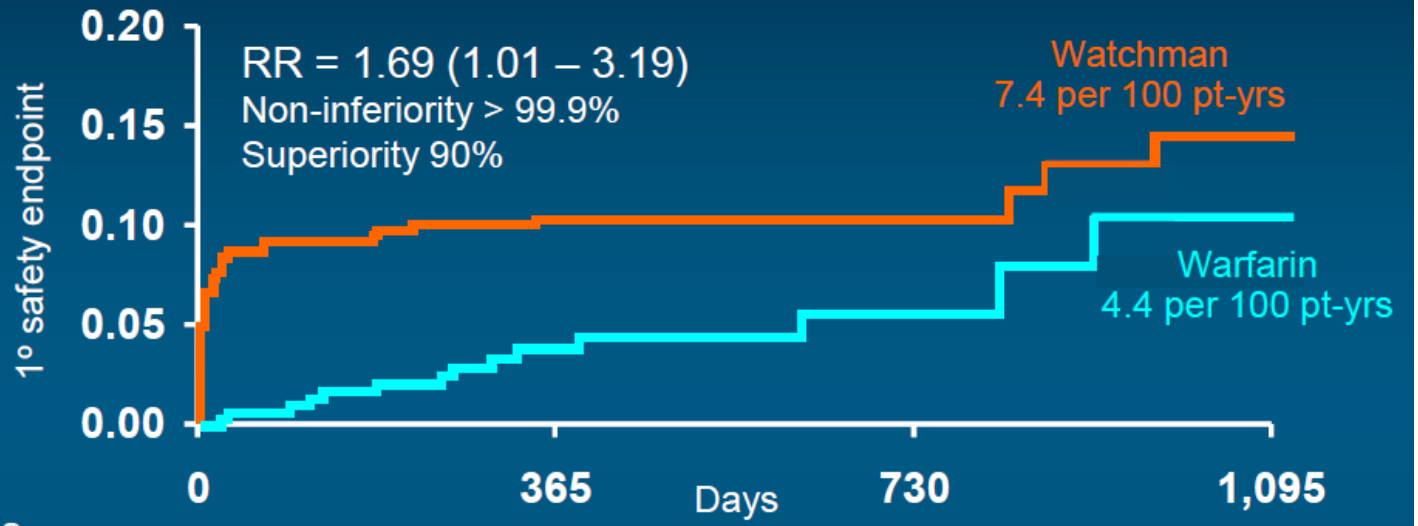


PROTECT-AF

Primary Safety and Efficacy Endpoints

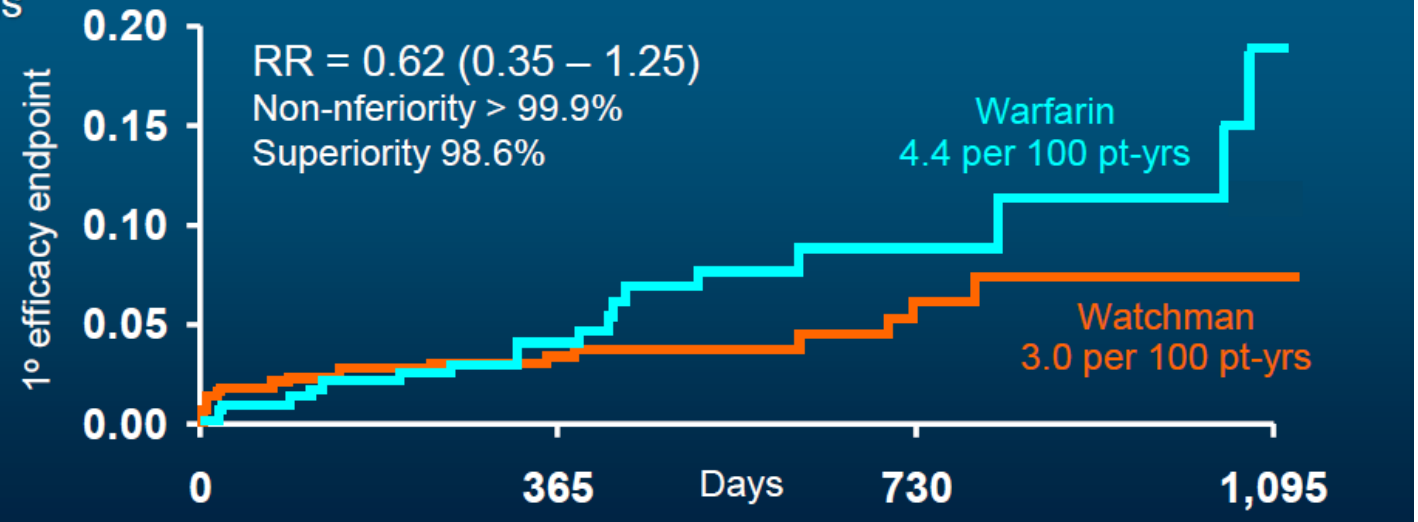
Major bleeding (IC, GI) Serious procedure related complications:

- Tamponade
- Device embolization
- Stroke



Intention-to-treat analysis

- All strokes
- CV deaths
- Unexplained death



Holmes DR, et al. Lancet 2009;374:534-42

LAA Closure/Occlusion/Excision

Recommendations for LAA closure/occlusion/excision		
Recommendations	**Class**	**Level**
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

FA et maladie athéromateuse stable

- Environ 30% des patients avec FA ont une maladie coronaire ou artérielle périphérique stable.
- Une pratique fréquente est de traiter ces patients par AVK et antiagrégant (aspirine en général)
- L'ajout d'aspirine aux AVK ne diminue pas le risque d'AVC ou d'évènements vasculaires (en particulier d'IDM)…
- …mais augmente franchement le risque hémorragique.

Camm AJ et al, *Eur Heart J* 2010;31:2369-429

Antithrombotic Therapy in AF Patients with ACS and/or Undergoing PCI/ Stenting

Table 11 Antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	Elective	Drug-eluting	3 (-olimus[a] group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score ≥3)	Elective	Bare-metal[c]	2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal[c]	4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone

AF - ESC Guidelines, *EHJ 2010*

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

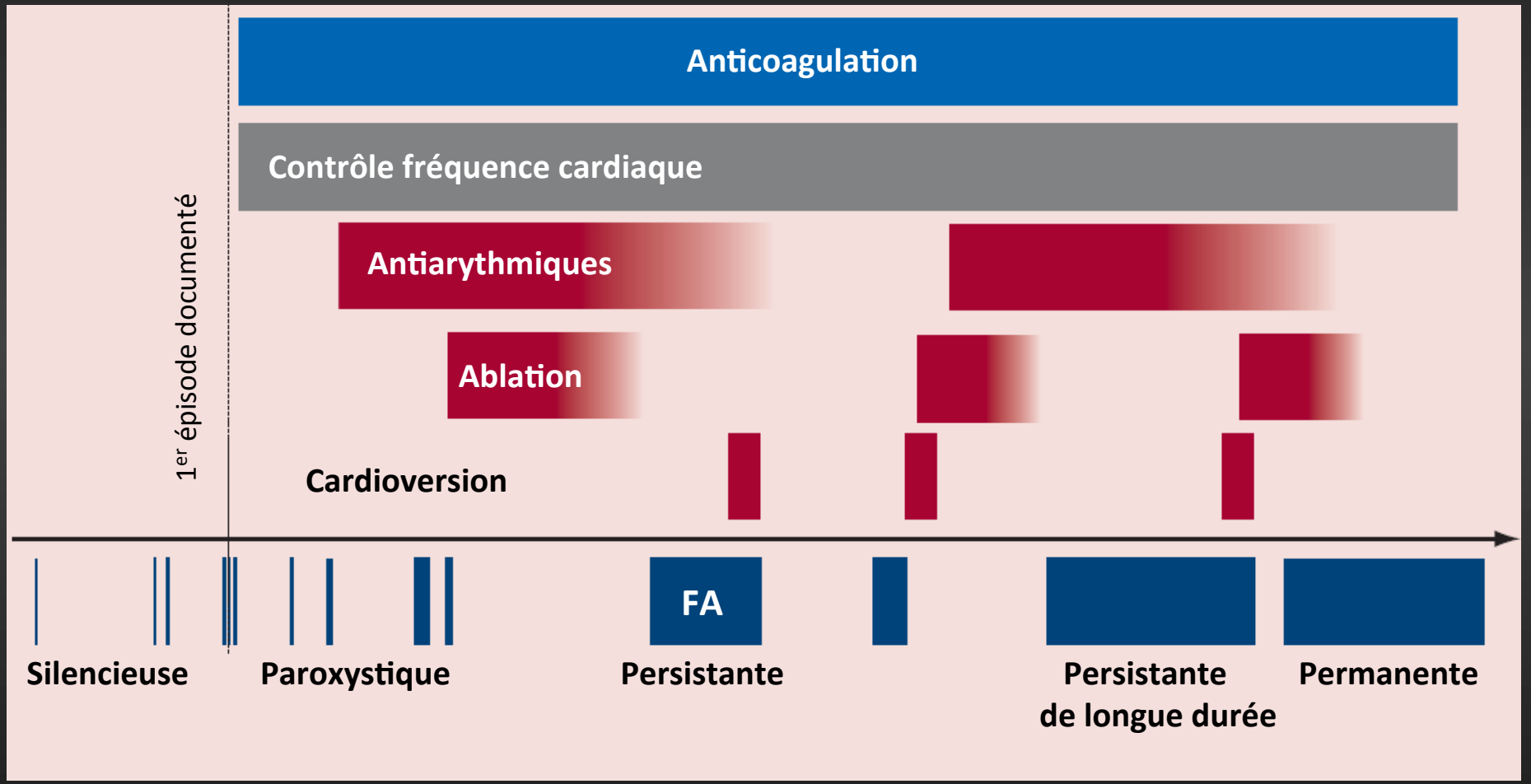
Olesen, Lip et al. *Thromb Hemostat 2011*

Table 2: Hazard ratios of thromboembolism at maximum 12 years follow-up

	Whole cohort (n=132,372)				No preMI (n=112,916)	With preMI (n=19,456)
	Years of exposure	TE events	Hazard ratio (CI)*	Hazard ratio (CI)‡ (Adjusted)	Hazard ratio (CI)‡ (Adjusted)	Hazard ratio (CI)‡ (Adjusted)
$CHADS_2$						
Low (score 0)						
VKA only	40,960	428	Reference	Reference	Reference	Reference
No treatment	82,214	1,280	1.53 (1.37–1.71)	2.09 (1.86–2.34)	2.09 (1.86–2.35)	2.10 (1.42–3.10)
ASA only	22,310	439	1.90	1.92	2.04	1.34
			(2.25–2.67)	(1.82–2.16)	(1.88–2.27)	(1.15–1.89)
VKA + ASA	9,685	230	1.34 (1.16–1.55)	1.41 (1.22–1.64)	1.47 (1.25–1.73)	1.09 (0.76–1.56)
High (2–6)						
VKA only	48,879	2,159	Reference	Reference	Reference	Reference
No treatment	60,550	5,100	1.92 (1.82–2.01)	1.82 (1.73–1.92)	1.88 (1.78–1.99)	1.56 (1.38–1.76)
ASA only	42,984	3,512	1.86	1.73	1.79	1.47
			(1.76–1.96)	(1.64–1.83)	(1.69–1.91)	(1.30–1.67)
VKA + ASA	12,590	606	1.00 (0.92–1.10)	1.05 (0.96–1.15)	1.05 (0.94–1.17)	1.00 (0.84–1.20)

"Acetylsalicylic acid should not be used for thromboprophylaxis in any patient with atrial fibrillation".

Conclusion



AF - ESC Guidelines, *EHJ 2010*

Conclusion

- L'évaluation du risque thrombo embolique dans la FA (score CHA_2DS_2VASc) et les recommandations récentes incitent à traiter une majorité de patients par anticoagulant oral.

- L'évaluation du risque hémorragique (score HAS BLED) n'a pas pour but de contrindiquer le traitement anticoagulant mais peut inciter à proposer une surveillance très attentive.

- La disponibilité des nouveaux anticoagulants oraux devrait aider à atteindre ces objectifs de traitement.