DAVOS CONGRESS

Cardiology Update
2013

EUROPEAN SOCIETY OF CARDIOLOGY®

Treatment Recommendations in Non Valvular Atrial Fibrillation

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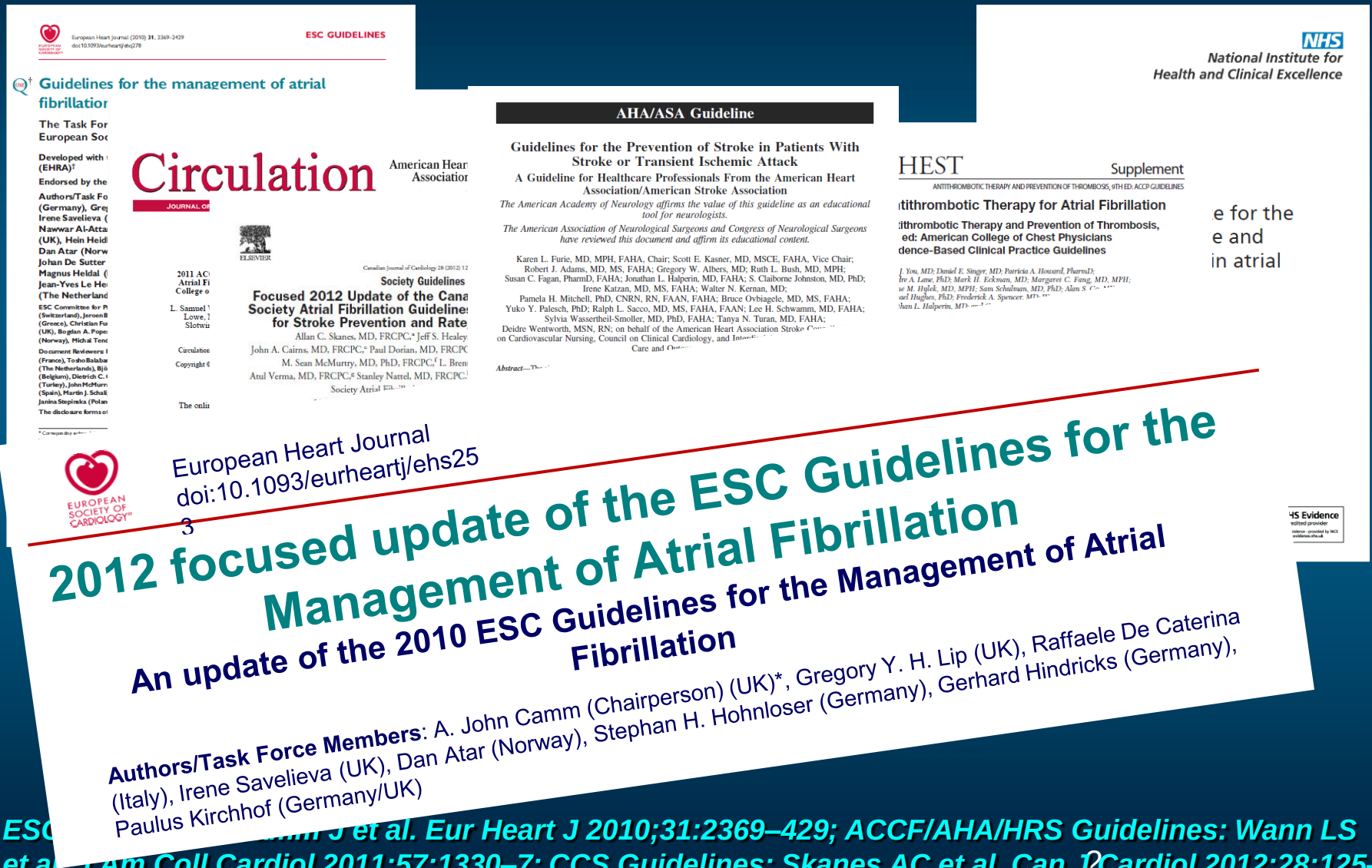
Advisor / Speaker : Astra Zeneca, Gilead, Merck, Menarini, Sanofi Aventis, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionics, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

Guidelines for AF Management



ESC ... J et al. Eur Heart J 2010;31:2369–429; ACCF/AHA/HRS Guidelines: Wann LS et al. J Am Coll Cardiol 2011;57:1330–7; CCS Guidelines: Skanes AC et al. Can J Cardiol 2012;28:125–136; You JY et al. ACCP Guidelines: Chest 2012;141;e531S–e575S; http://www.nice.org.uk/ta249

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

Camm AJ, et al. European Heart Journal 2012; 33: 2719-47
Camm AJ, et al. EP Europace 2012; 14: 1385-413

CHA_2DS_2-VASc
Assessment of Thromboembolic Risk

- **C**ongestive heart failure/ dysfunction **1** LV
- **H**ypertension **1**
- **A**ge ≥ 75 **2**
- **D**iabetes mellitus **1**
- **S**troke/TIA/TE **2**
- **V**ascular disease (CAD, AoD, PAD) **1**
- **A**ge 65-74 **1**
- **S**ex **c**ategory (female) **1**

Score 0 – 9

Validated in 1084 NVAF patients not on OAC with known TE status at 1 year in Euro Heart Survey

OR for stroke if:
Female: 2.53 (1.08 – 5.92), p=0.029;
Vascular disease: 2.27 (0.94 – 5.46), p=0.063

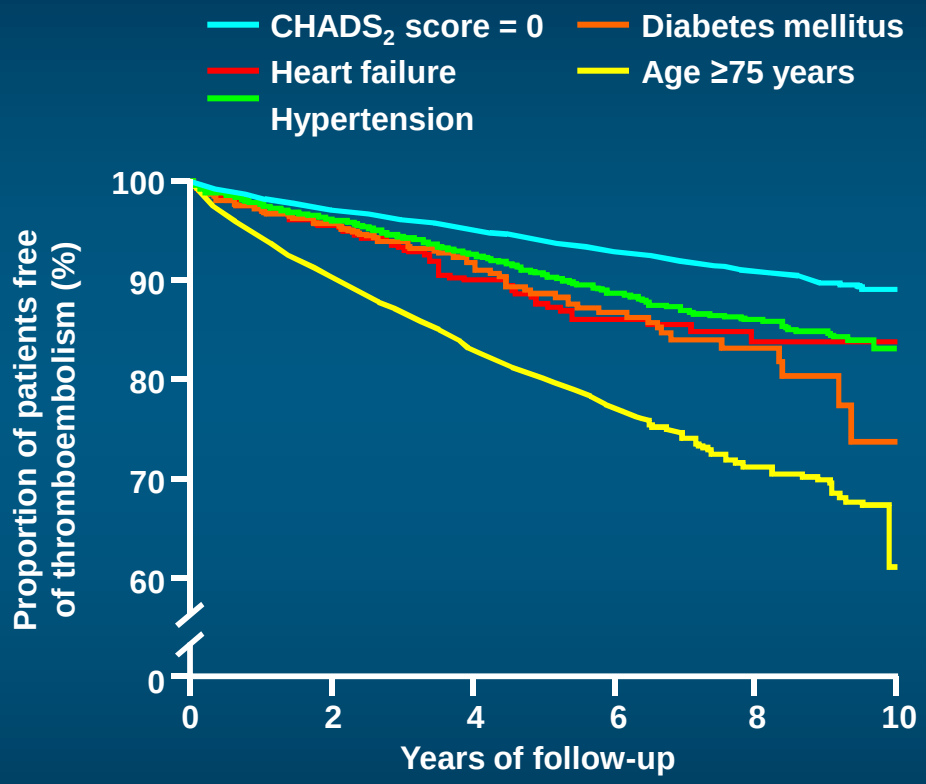
Score	Annual stroke rate, %	
n	1084	73 538
0	0	0.78
1	1.3	2.01
2	2.2	3.71
3	3.2	5.92
4	4.0	9.27
5	6.7	15.26
6	9.8	19.78
7	9.6	21.50
8	6.7	22.38
9	15.2	23.64

Lip GYH, et al. Chest 2009

Olesen JB et al. BMJ 2011;342:124

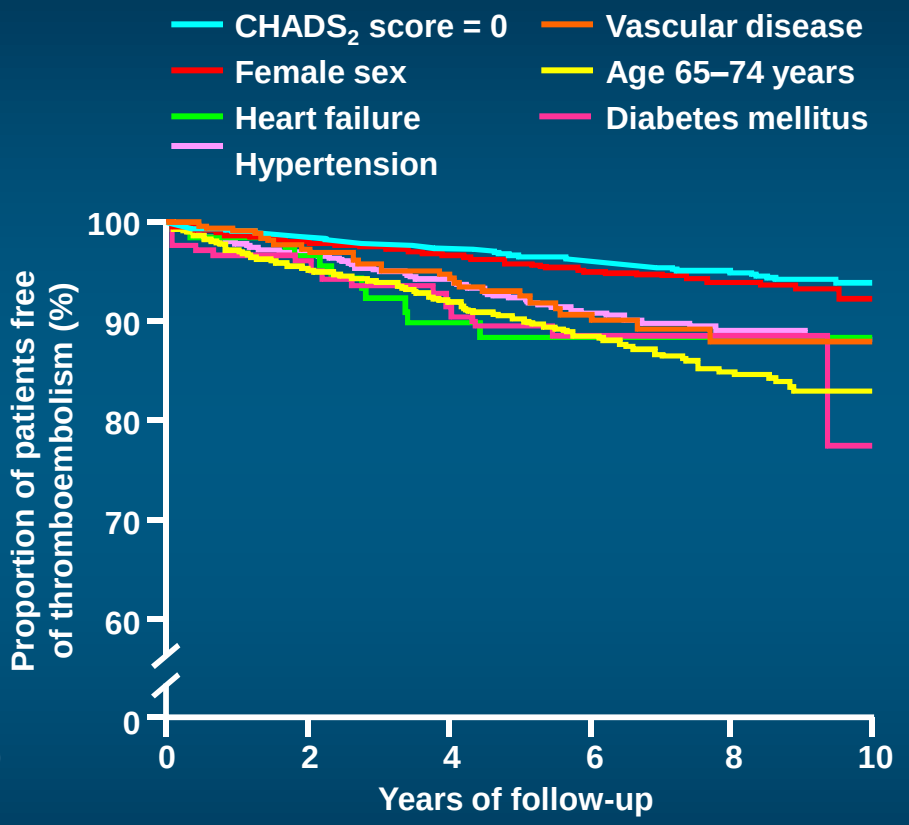
$CHADS_2$ vs CHA_2DS_2VASc

All patients with atrial fibrillation not treated with VKAs in Denmark 1997- 2006



Kaplan-Meier estimate of probability of remaining free of thromboembolism with $CHADS_2$ score 0 and 1. Only patients with $CHADS^2$ scores 0 and 1 were included, and patients were censored at death for causes other than thromboembolism

73 538 fulfilled the study inclusion criteria



Kaplan-Meier estimate of probability of remaining free of thromboembolism with CHA_2DS_2 score 0 and 1. Only patients with CHA_2DS_2 scores 0 and 1 were included, and patients were censored at death for causes other than thromboembolism

Olesen JB et al, BMJ 2011;342:d124

Annual unadjusted incidence rates of thromboembolism among men and women with AF not taking warfarin *

Risk factor		Annual thromboembolism rate (95% CI)	
		Women	Men
Age ≥75 y		5.0 (4.3–5.7)	2.8 (2.3–3.4)
Prior ischemic stroke		9.7 (7.0–13.6)	7.3 (5.2–10.3)
Diagnosed hypertension		4.0 (3.4–4.7)	2.4 (2.0–3.0)
Diagnosed congestive heart failure		5.7 (4.7–6.9)	2.5 (1.9–3.2)
Diagnosed coronary artery disease		4.7 (3.8 –6.0)	2.4 (1.9–3.1)
Diabetes mellitus		5.0 (3.7–6.6)	3.1 (2.3–4.2)
$CHADS_2$ score	0	0.6 (0.2–1.2)	0.5 (0.3–0.9)
	1	1.8 (1.3–2.4)	1.2 (0.9–1.7)
	2	4.4 (3.6–5.4)	1.9 (1.4–2.6)
	3	6.1 (4.8–7.8)	3.9 (2.8–5.3)
	4	9.1 (6.2–13.3)	6.5 (4.2–10.0)
	5	7.7 (3.6–16.5)	2.6 (0.8–8.1)
	6	11.4 (2.5–51.9)	16.2 (7.4–35.6)

* $CHADS_2$ score calculated by assigning 2 points to prior stroke or transient ischemic attack and 1 point to any of the following risk factors: congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus

Fang M, et al. Circulation 2002:112:1687-91

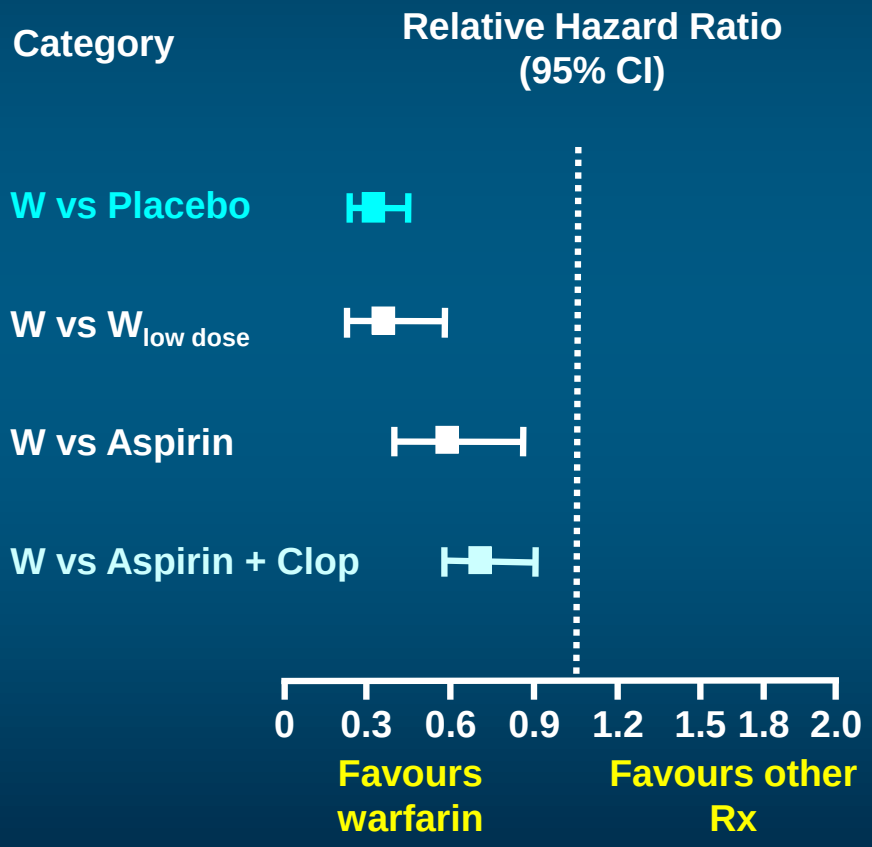
Recommendations relating to Stroke Risk

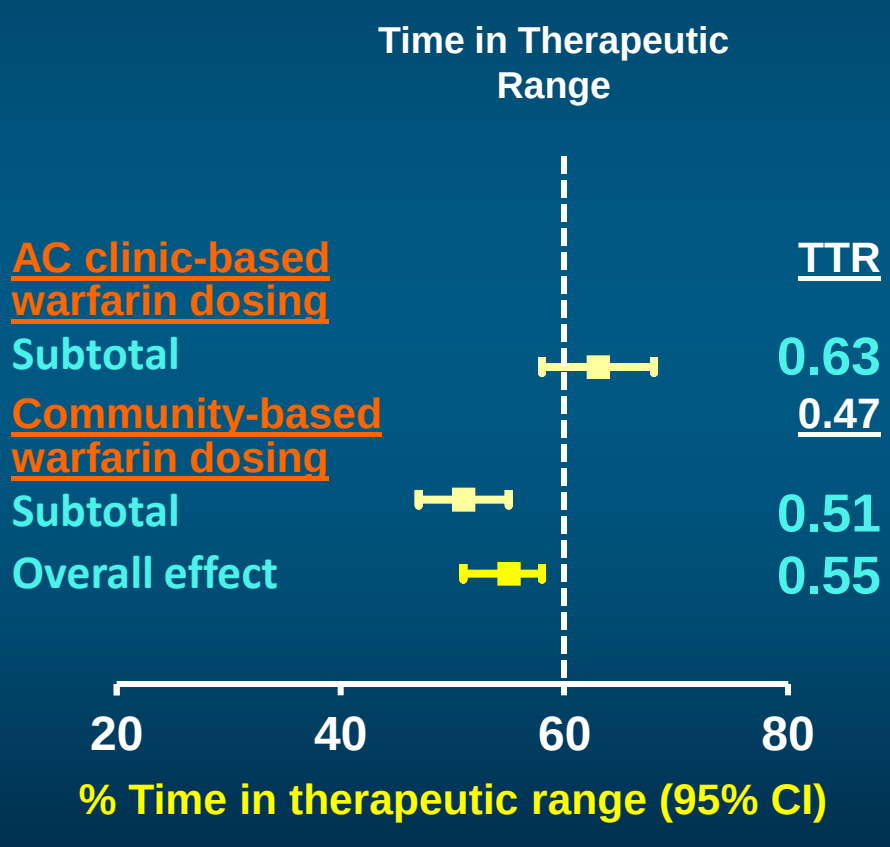
Recommendations	Class	Level
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. is recommended, unless contraindicated.	I	A
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A

[d] = pending EMA/FDA approval – prescribing information is awaited

Camm AJ, et al. European Heart Journal 2012; 33: 2719-47
Camm AJ, et al. EP Europace 2012; 14: 1385-413

Warfarin (or Any Coumarin)
An Effective but Badly used Therapy





Modified from Camm A.J. EHJ 2009;30:2554-5

J Manag Care Pharm 2009;15(3):244-52

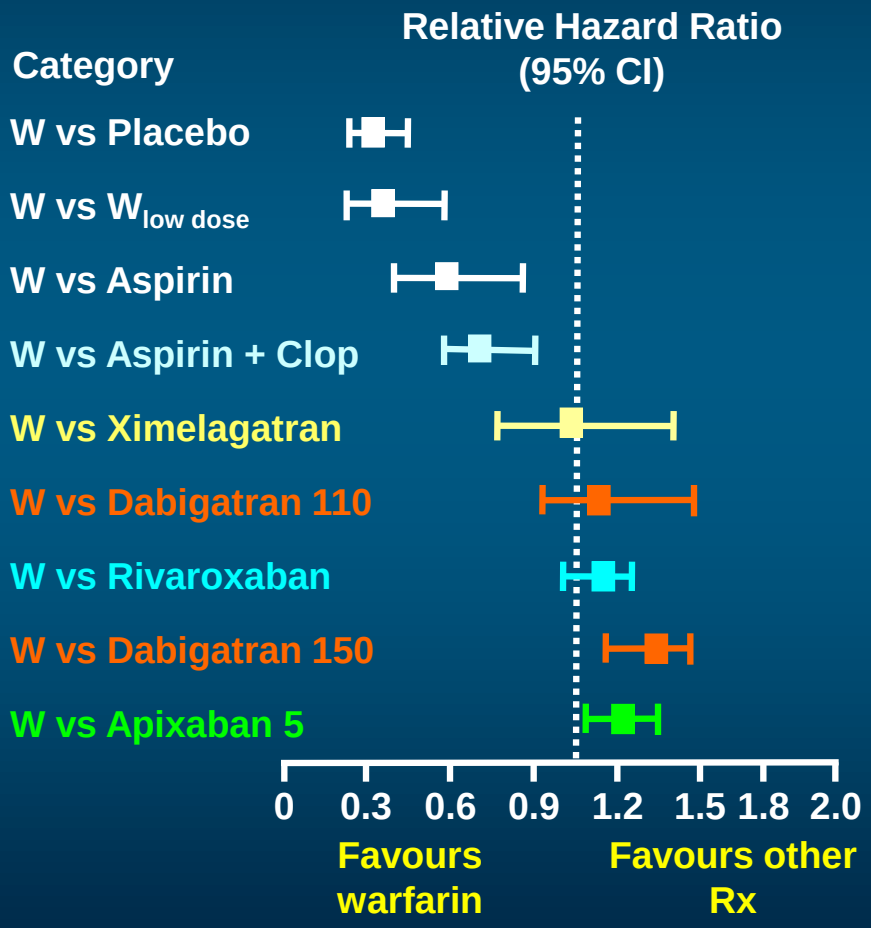
By any other name ……!

Coumadin (Warfarin)

Synonyms: *Uniwarfin, Athrombin, Brumolin, Co-Rax, Coumafen, Coumaphen, Coumarin, Coumefene, D-Con, Dethmor Dethnel, Dicusat E, Fasco Fascrat Powder, Frass-Ratron, Jantoven, Killgerm Sewarin P, Kumader, Kumadu, Kumatox, Kypfarin, Latka 42, Liqua-Tox, Maag Rattentod Cum, Mar-Frin, Marevan, Maveran, Mice Bait, Mouse Pak, Panwarfin, Place-Pax, Prothromadin, Rodafarin, Rodex, Rosex, Sofarin, Solfarin, Sorexa Plus, Temus W, Tintorane, Tox-Hid, Vampirinip, Waran, Warf 42, Warfarat, Warficide, Warfilone, Zoocoumarin*

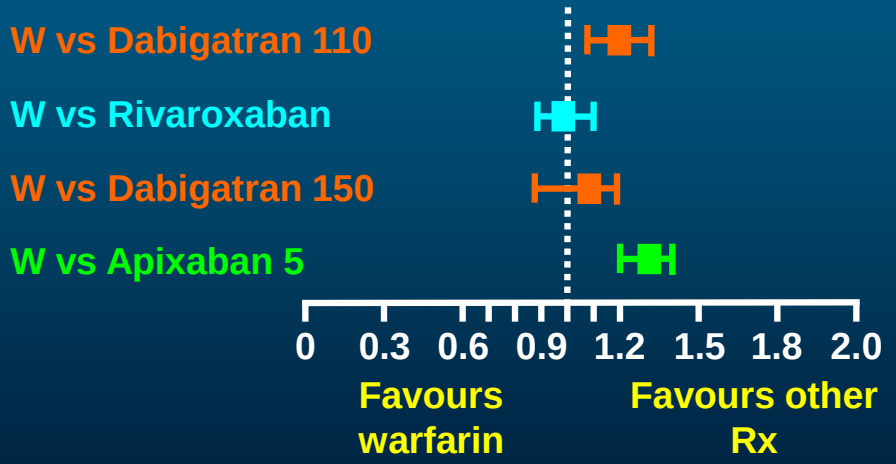
Stroke Prevention: OAC Effect

Stroke or systemic embolism



Intracranial haemorrhage

Major bleeding



Modified from Camm A.J. EHJ 2009;30:2554-5

Anticoagulation - NOACs

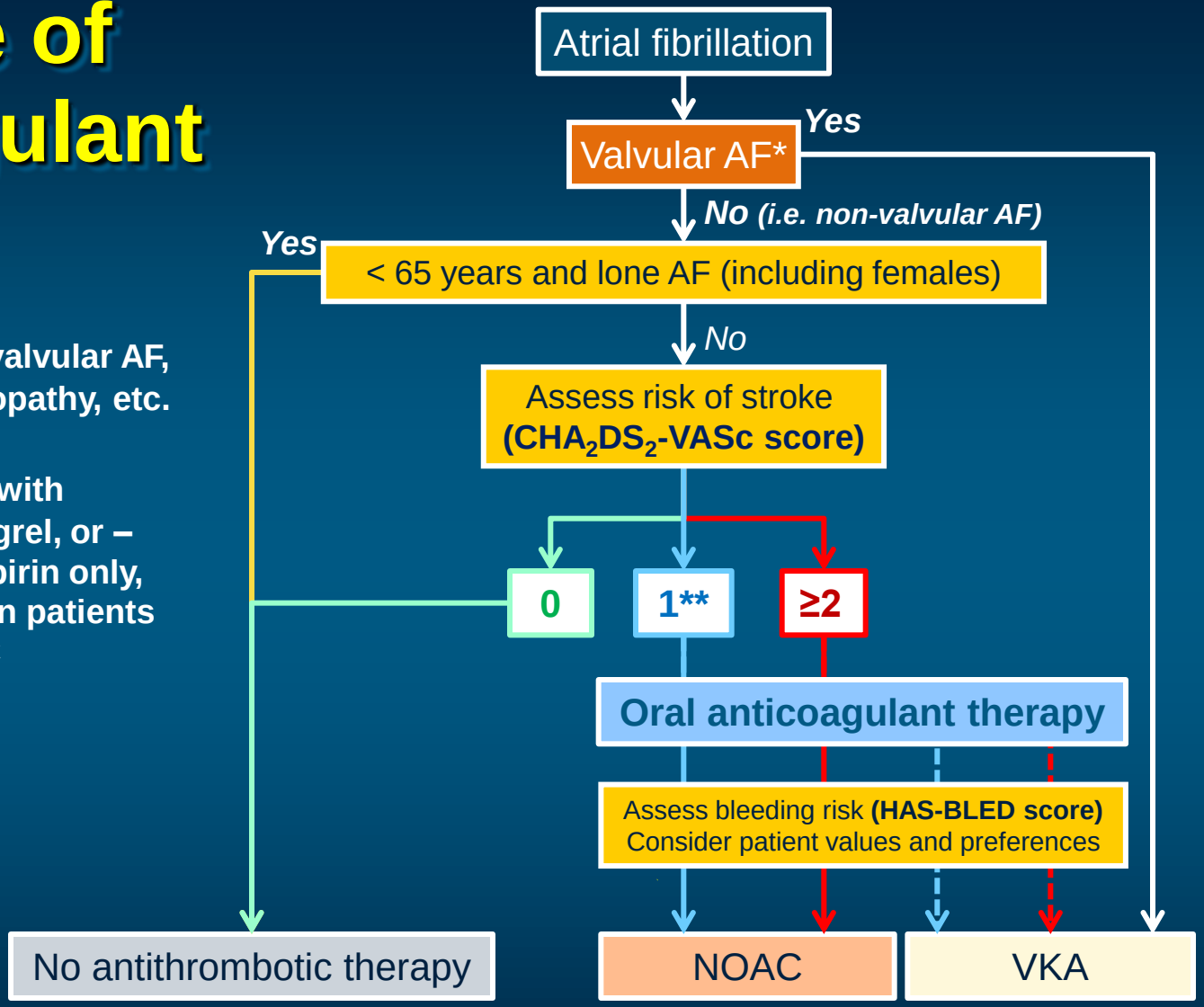
Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	**Class**	**Level**
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

Camm AJ, et al. European Heart Journal 2012; 33: 2719-47
Camm AJ, et al. EP Europace 2012; 14: 1385-413

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



Camm AJ, et al. European Heart Journal 2012; 33: 2719-47
Camm AJ, et al. EP Europace 2012; 14: 1385-413

ACCF/AHA/HRS Focused Update Recommendations for Dabigatran

2011 Focused Update Recommendation	Comments
Class I Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function). (***Level of Evidence: B***)	**New recommen-dation**

Wann LS et al. J Am Coll Cardiol 2011;57:1330–7

ACCP 9 Antithrombotic Therapy for AF

… patients with nonrheumatic AF, <u>including those with paroxysmal AF</u>, who are:

Low risk	*Intermediate risk*	*High risk*
e.g. $CHADS_2 = 0$	e.g. $CHADS_2 = 1$	e.g. $CHADS_2 \geq 2$
No antithrombotic therapy (2,B)	Oral anticoagulant therapy (1,B)	Oral anticoagulant therapy (1,A)
Aspirin 75–325 mg/d (2,B)	Aspirin plus clopidogrel (2,B)	Aspirin plus clopidogrel (1,B)

preferred option
patient preference
if OAC contraindicated for other than bleeding

Dabigatran 150 mg b.i.d. preferred to Dose adjusted VKA (2,B)

"….AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), …. antithrombotic therapy decisions follow the general risk-based recommendations …. , <u>regardless of the apparent persistence of normal sinus rhythm</u> (2,C)"

You JJ et al. CHEST 2012; 141(2)(Suppl):e531S–e575S

AHA/ASA 2012 Update SPAF and OAC

1. **Warfarin *(Class I; Level of Evidence A)*, dabigatran *(Class I; Level of Evidence B)*, apixaban *(Class I; Level of Evidence B)*, and rivaroxaban *(Class IIa; Level of Evidence B)***

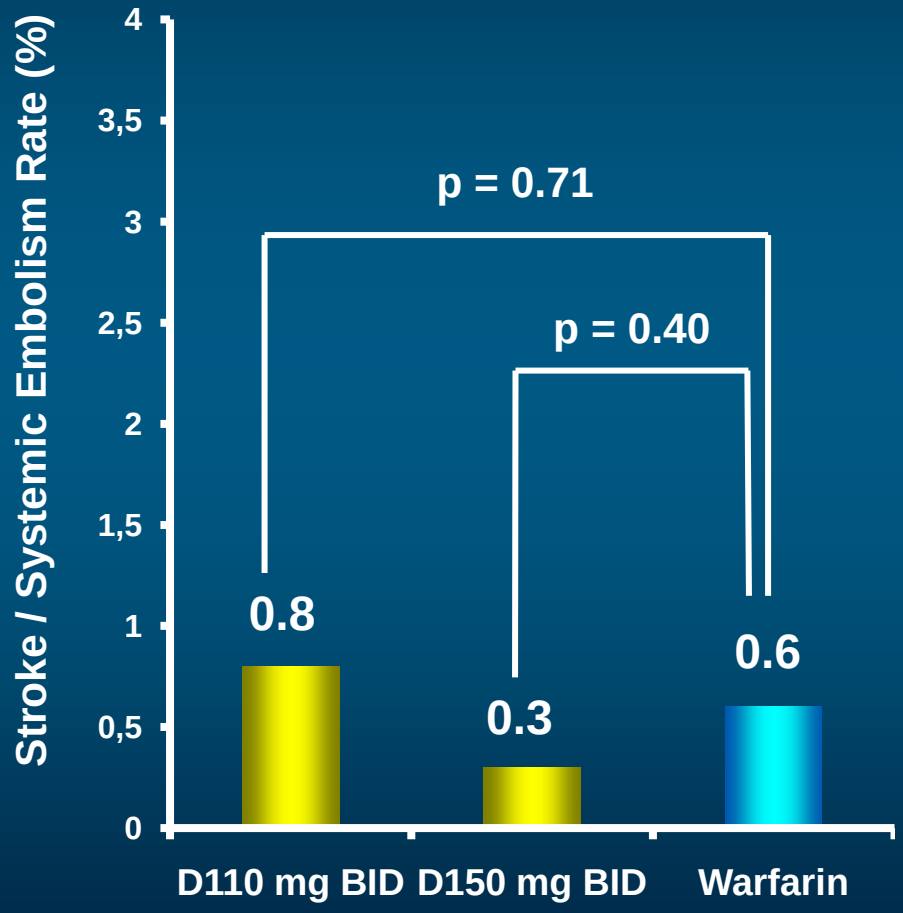
are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF.

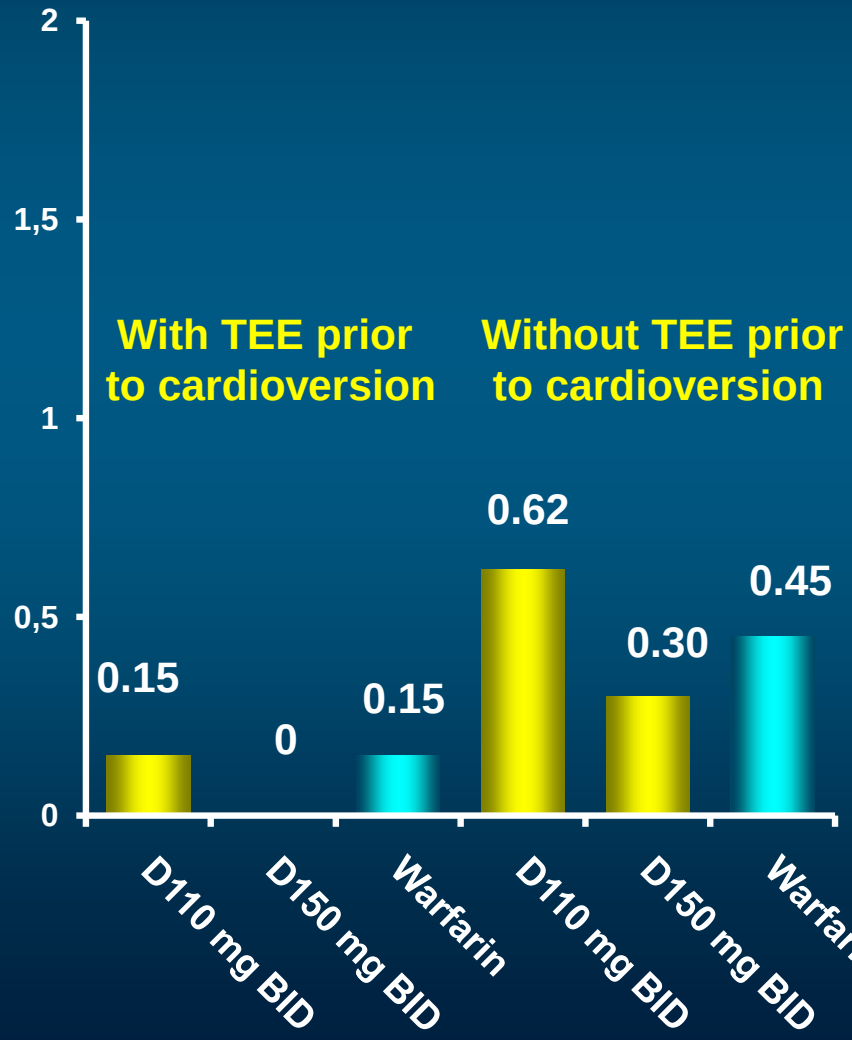
The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin.

Furie KL, et al. http://stroke.ahajournals.org/content/early/2012/08/02/STR.0b013e318266722a.citation

Dabigatran - Stroke and Systemic Embolism after Cardioversion

1983 cardioversions were performed in 1270 patients





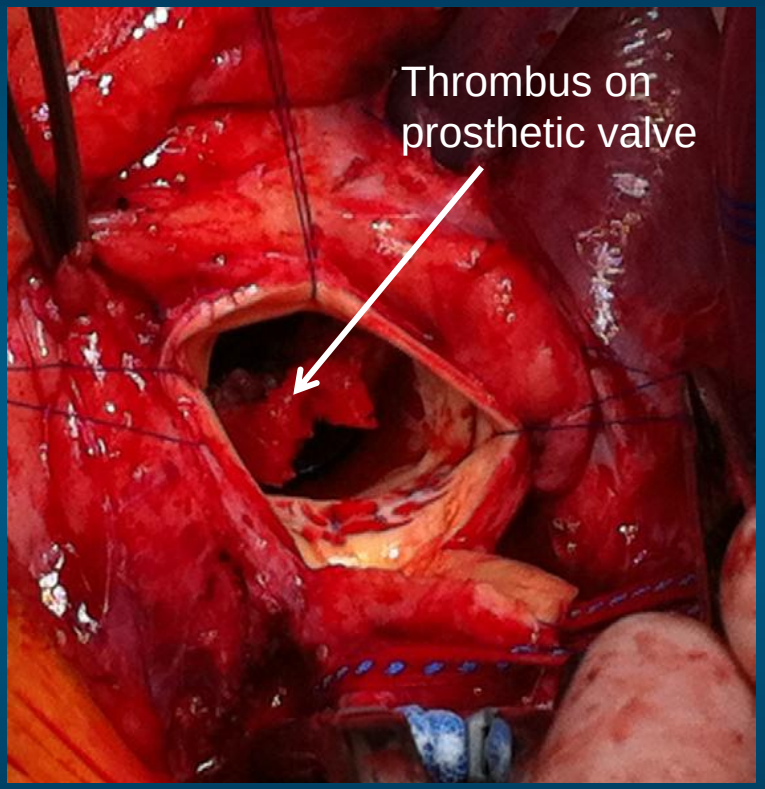
Nagarakanti R et al. *Circulation. 2011;123:131-136*

Anticoagulation - Cardioversion

Recommendations for prevention of thromboembolism in non-valvular AF – Peri-cardioversion		
Recommendations	**Class**	**Level**
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g., **VKA with INR 2-3 or dabigatran**) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B
In patients with risk factors for stroke, OAC therapy, whether with **dose-adjusted VKA (INR 2-3) or a NOAC**, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B

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

Valve Thrombosis on Dabigatran



51-year-old woman
4-week progressive exertional dyspnoea
Mechanical AVR 8 years ago
Two months ago GP switched her from warfarin to dabigatran (150 mg b.i.d.) for mechanical valve anticoagulation.

A 59-year-old woman
Mechanical mitral valve 5 years ago
Routine follow-up
3 months previously switched by GP from warfarin to dabigatran 150 mg b.i.d.)
Progressive dyspnoea
Echo showed large thrombus

RE-ALIGN--a phase 2 dose-finding trial with dabigatran in patients with mechanical valves, employing doses of 150 to 330 mg b.i.d., adjusted based on renal function and the results of the **Hemoclot** **has now been discontinued** for hazard associated with dabigatran

Price J, et al. J Amer Coll Cardiol http://dx.doi.org/10.1016/j.jacc.2012.06.039

Cardiac Events During RE-LY ITT Analysis

	Dabigatran 150 v Warfarin			All Dabigatran versus Warfarin		
	HR	95% CIs	p	HR	95% CIs	p
Total MI	1.27	0.94–1.71	0.12	1.28	0.98–1.67	0.07
Clinical MI	1.32	0.96–1.81	0.09	1.31	0.99–1.74	0.06
Silent MI	0.87	0.34–2.27	0.72	1.04	0.47–2.31	0.92
Cardiac death	0.91	0.73–1.12	0.37	0.96	0.80–1.15	0.64
Cardiac arrest	0.98	0.56–1.70	0.94	0.94	0.58–1.53	0.81
MI, UA, cardiac arrest, or cardiac death	0.98	0.85–1.12	0.77	0.95	0.84–1.07	0.42

Honhloser S et al. Circulation. 2012;125:669-676

Mortality and Net Benefit
RELY-ABLE

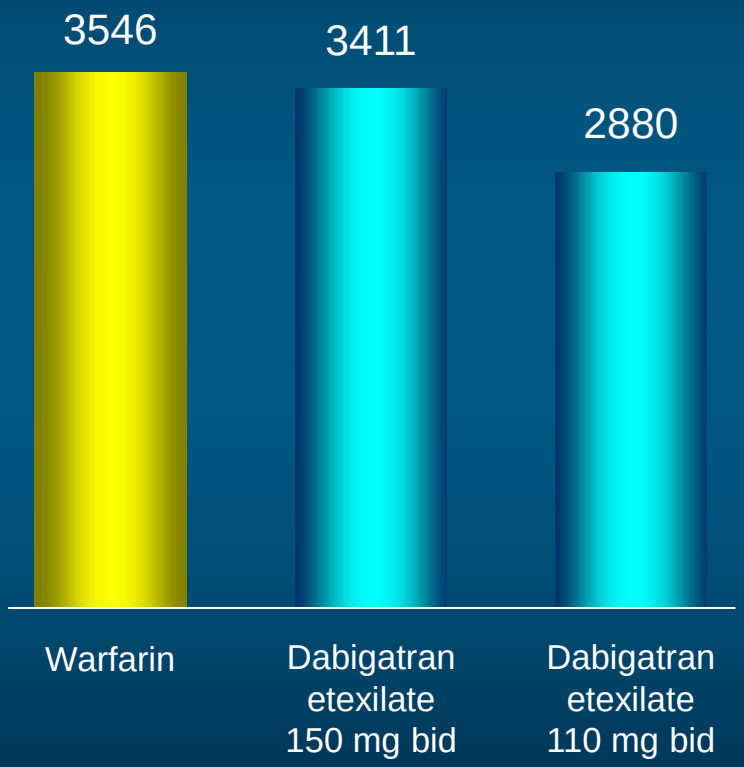
Event	RELY-ABLE			
	110 mg (%/yr)	150 mg (%/yr)	HR	95% CI
Total mortality	3.10	3.02	0.97	0.80-1.19
Vascular mortality	1.62	1.67	1.03	0.78-1.35
Disabling stroke, life-threatening bleed or death	4.45	4.53	1.02	0.86-1.20
Stroke, systemic embolism, myocardial infarction, pulmonary embolism, major bleed or death	**6.89**	**7.36**	**1.07**	**0.94-1.22**

5851 patients followed for mean of 2.25 years

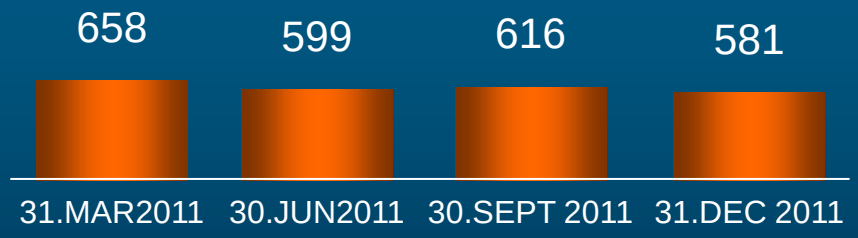
Connolly S, et al. AHA 2012

Serious Bleeds in RE-LY versus Real-world

Incidence rate in RE-LY per 100,000 patient years



Reporting rate with Dabigatran etexilate In real-world per 100,000 patient years



Connolly SJ, et al. N Engl J Med 2009;361:1139-51; Boehringer Ingelheim, RE-LY® database, analysis of events while on treatment (Safety analysis set); Data from Boehringer Ingelheim drug safety database, 31. December 2011

FDA Announcement

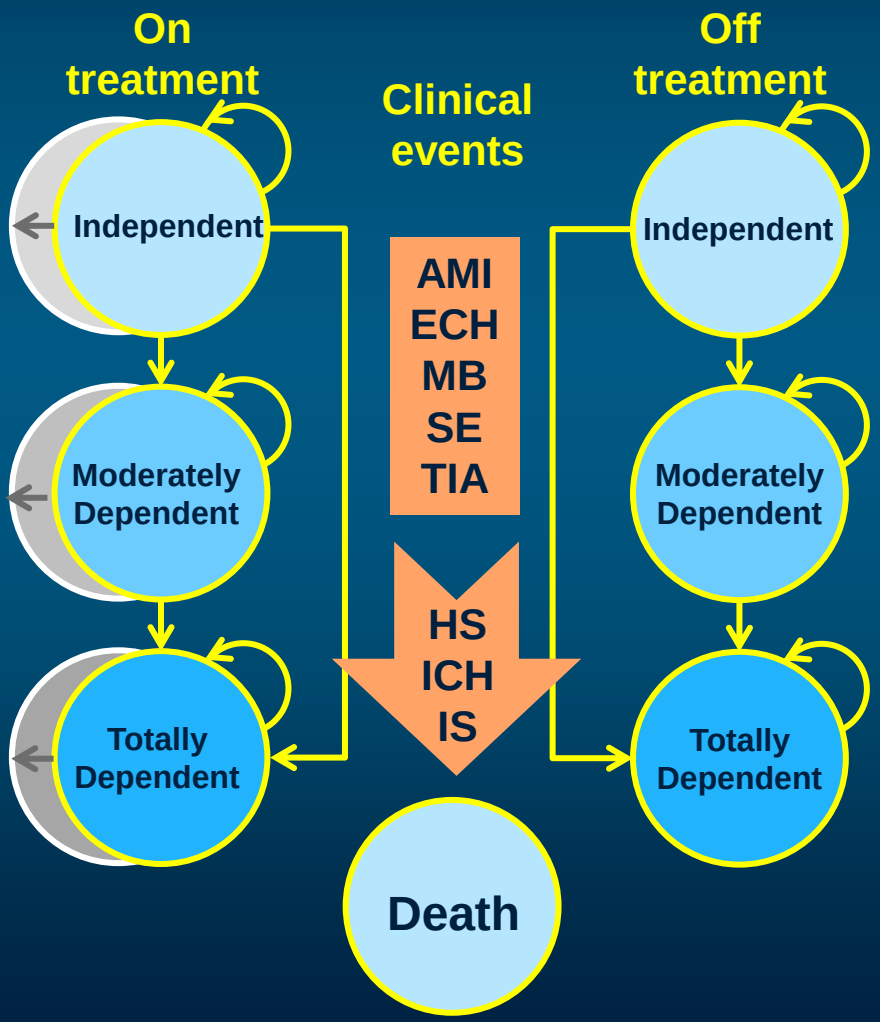
For the populations in the Mini-Sentinel data assessment:

- The combined incidence rate (ICH and GIH events per 100,000 days at risk) was 1.8 to 2.6 times higher for new users of warfarin than for new users of Pradaxa
- The incidence rate of GIH events only per 100,000 days at risk was 1.6 to 2.2 times higher for warfarin new users than for Pradaxa new users
- The incidence rate of ICH events only per 100,000 days at risk was 2.1 to 3.0 times higher with warfarin than with Pradaxa

The results indicate that the observed bleeding rates associated with new use of Pradaxa do not appear to be higher than the bleeding rates associated with new use of warfarin.

Cost-Effectiveness of NOAC Therapy

Markov model simulating treatment and clinical events in two treatment arms over the lifetime of patients adapted to the **Swiss context,** including cost of anticoagulation therapy and clinical events in Switzerland.



Schedule	Dabigatran 110mg bid	Dabigatran 150mg bid	150 bid then 110 bid
Incremental QALY	1.848	2.433	2.774
Incremental Costs/life year	418	212	241
ICER (CHF)	25,108	9,708	10,215

Pletscher M, et al. Swiss Med Wkly 2013;143:w13732

Summary of NOAC Phase III Results

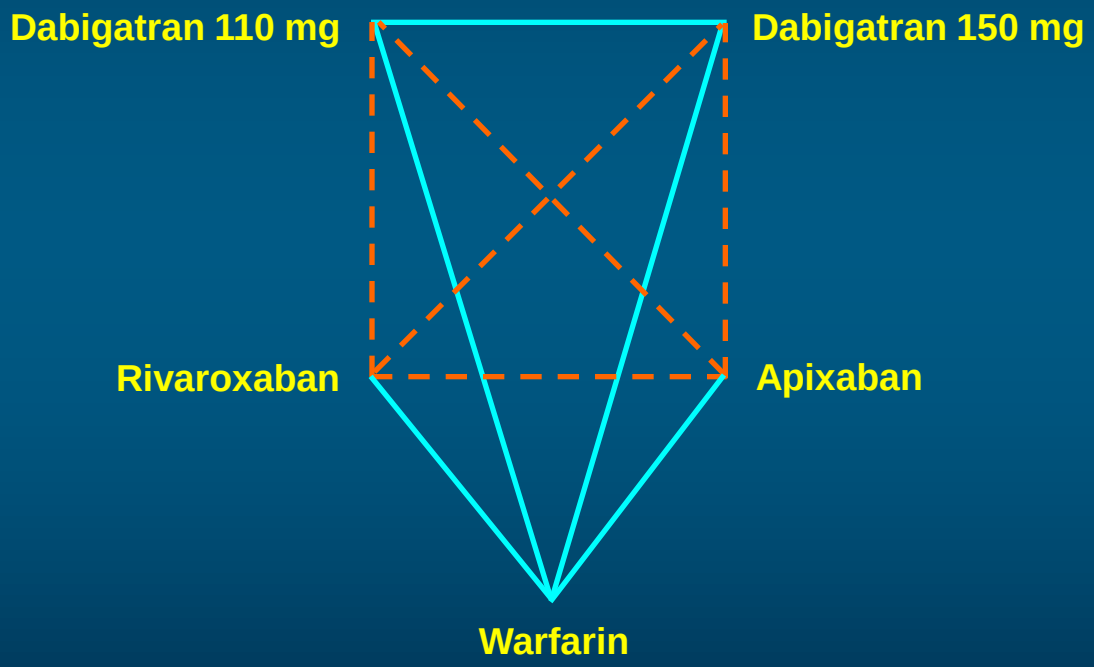
Outcomes *vs.* warfarin		Dabigatran 110 mg bid	Dabigatran 150 mg bid	Rivaroxaban 20 mg od
↓ in stroke/ systemic embolism	Intention to treat population	Non-inferiority	Superiority	Non-inferiority
	On treatment population			Superiority
↓ in stroke		No	Yes	No
↓ in ischaemic/unspecified stroke		No	Yes	No
↓ in haemorrhagic stroke		Yes	Yes	Yes
↓ in disabling/fatal stroke		No	Yes	No
↓ in vascular death		No	Yes	No
↓ in all-cause death		No	No	No
↓ in major bleeding		Yes	No	No
↓ in ICH		Yes	Yes	Yes
↑ in GI bleeding		No	Yes	Yes

1. Connolly et al. NEJM 2010;363:1875-6. 2. Patel et al. NEJM 2011;365:883-91. 3. Granger et al. NEJM 2011;365:981-92.

Network Meta-Analysis of NOACs

- Multiple publications using the **network meta-analysis** method have been published so far.[1-5]
- These analyses yielded comparable findings.

Graphical presentation derived from the work of Fadda et al.[4,6]



1. Harenberg et al. Intern Angiol 2012;31:330-9.
2. Schneeweiss et al. Circ Cardiovasc Qual Outcomes 2012;5:480-6.
3. Lip et al. J Am Coll Cardiol 2012;;60:738-46.
4. Mantha & Ansell. Thromb Haemost 2012;e-published June 28.
5. Wells et al. April 2012. Available at: http://www.cadthca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf. Accessed 29/08/12.
6. Fadda et al. BMJ 2011;342;d1555.

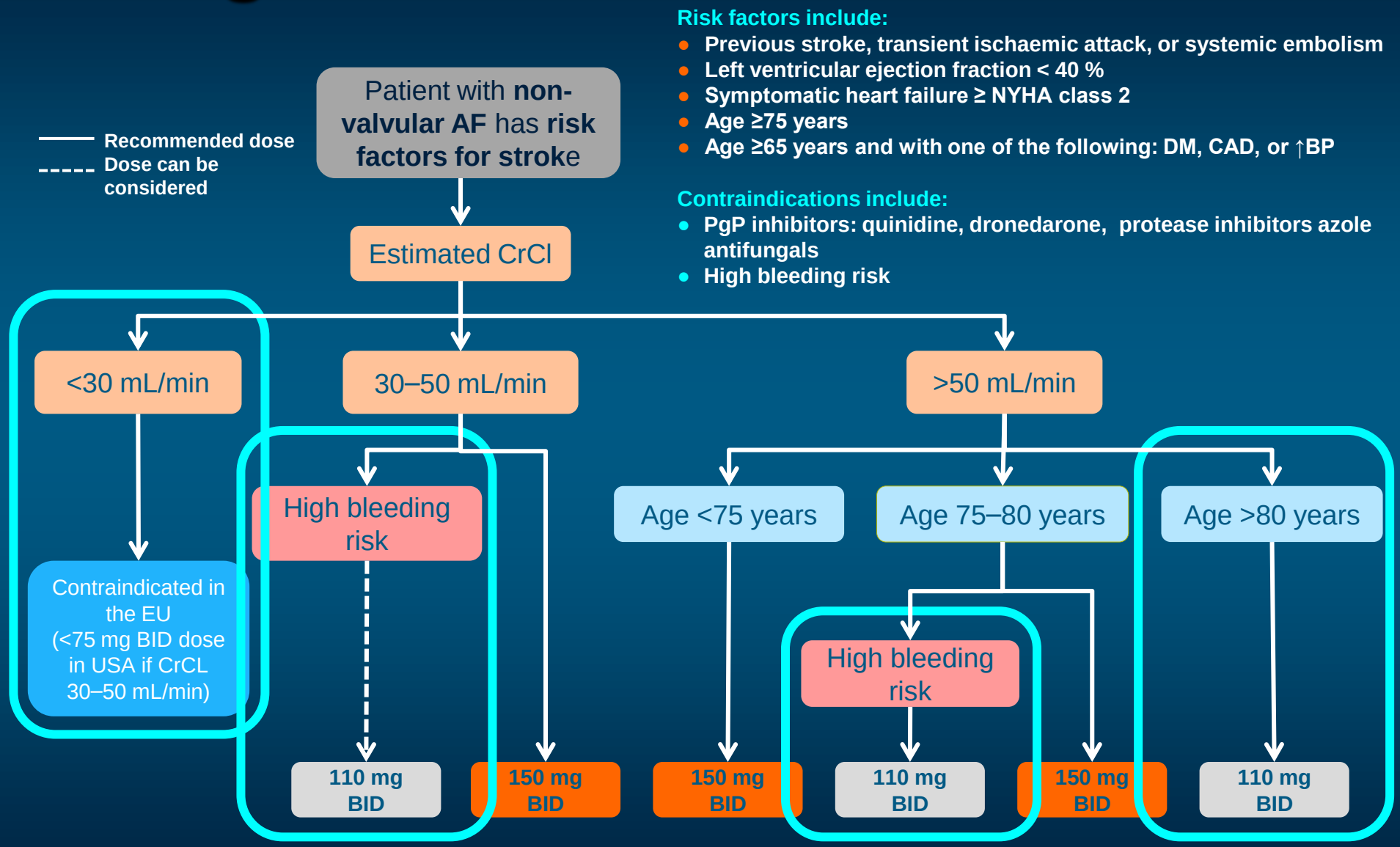
Indirect Treatment Analysis

Table 4 Indirect Comparison Using Warfarin as Single Common Comparator, on the Basis of the RE-LY, ROCKET-AF, and ARISTOTLE Trials

	Apixaban ← → Dabigatran 110		Apixaban ← → Dabigatran 150		Apixaban ← → Rivaroxaban		Dabigatran 110 ← → Rivaroxaban		Dabigatran 150 ← → Rivaroxaban	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67–1.15)	1.22	(0.91–1.62)	0.90	(0.71–1.13)	1.02	(0.79–1.32)	**0.74**	**(0.56–0.97)**
Stroke	0.86	(0.65–1.14)	1.23	(0.92–1.66)	0.93	(0.71–1.22)	1.08	(0.81–1.44)	0.75	(0.56–1.02)
Ischemic or uncertain type of stroke	0.83	(0.61–1.13)	1.21	(0.88–1.67)	0.98	(0.72–1.33)	1.18	(0.86–1.62)	0.81	(0.58–1.13)
Hemorrhagic stroke	1.65	(0.81–3.34)	1.96	(0.94–4.08)	0.86	(0.48–1.57)	0.53	(0.25–1.12)	**0.44**	**(0.20–0.96)**
Systemic embolism	NA		NA		**3.78**	**(1.16–12.31)**	NA		NA	
Nondisabling stroke	NA		NA		NA		0.83	(0.53–1.32)	**0.60**	**(0.37–0.97)**
Mortality endpoints										
Death from any cause	0.98	(0.83–1.16)	1.01	(0.85–1.20)	1.05	(0.84–1.30)	1.07	(0.85–1.34)	1.04	(0.82–1.30)
Death from vascular causes	NA		NA		NA		1.01	(0.78–1.31)	0.96	(0.74–1.24)
Other endpoints										
Myocardial infarction	0.68	(0.45–1.03)	0.69	(0.46–1.05)	1.09	(0.74–1.60)	**1.59**	**(1.07–2.37)**	**1.57**	**(1.05–2.33)**
Pulmonary embolism	0.62	(0.17–2.20)	0.48	(0.14–1.68)	NA		NA		NA	
Bleeding endpoints										
Major bleeding	0.86	(0.7–1.06)	**0.74**	**(0.61–0.91)**	**0.66**	**(0.54–0.81)**	**0.77**	**(0.63–0.94)**	0.89	(0.73–1.09)
Major or clinically relevant nonmajor bleeding	NA		NA		**0.66**	**(0.58–0.75)**	NA		NA	
Life-threatening bleeding	NA		NA		NA		1.36	(0.82–2.27)	1.62	(0.97–2.70)
Intracranial bleeding	1.35	(0.79–2.32)	1.05	(0.63–1.76)	0.63	(0.39–1.01)	**0.46**	**(0.27–0.80)**	0.60	(0.35–1.01)
Gastrointestinal bleeding	0.81	(0.57–1.15)	**0.59**	**(0.42–0.83)**	NA		NA		NA	
Extracranial or unclassified bleeding	0.84	(0.67–1.05)	**0.74**	**(0.59–0.92)**	NA		NA		NA	

Lip G, et al. J Am Coll Cardiol 2012;60:xxx

Dabigatran for SPAF in Switzerland



Risk factors include:

- Previous stroke, transient ischaemic attack, or systemic embolism
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure ≥ NYHA class 2
- Age ≥75 years
- Age ≥65 years and with one of the following: DM, CAD, or ↑BP

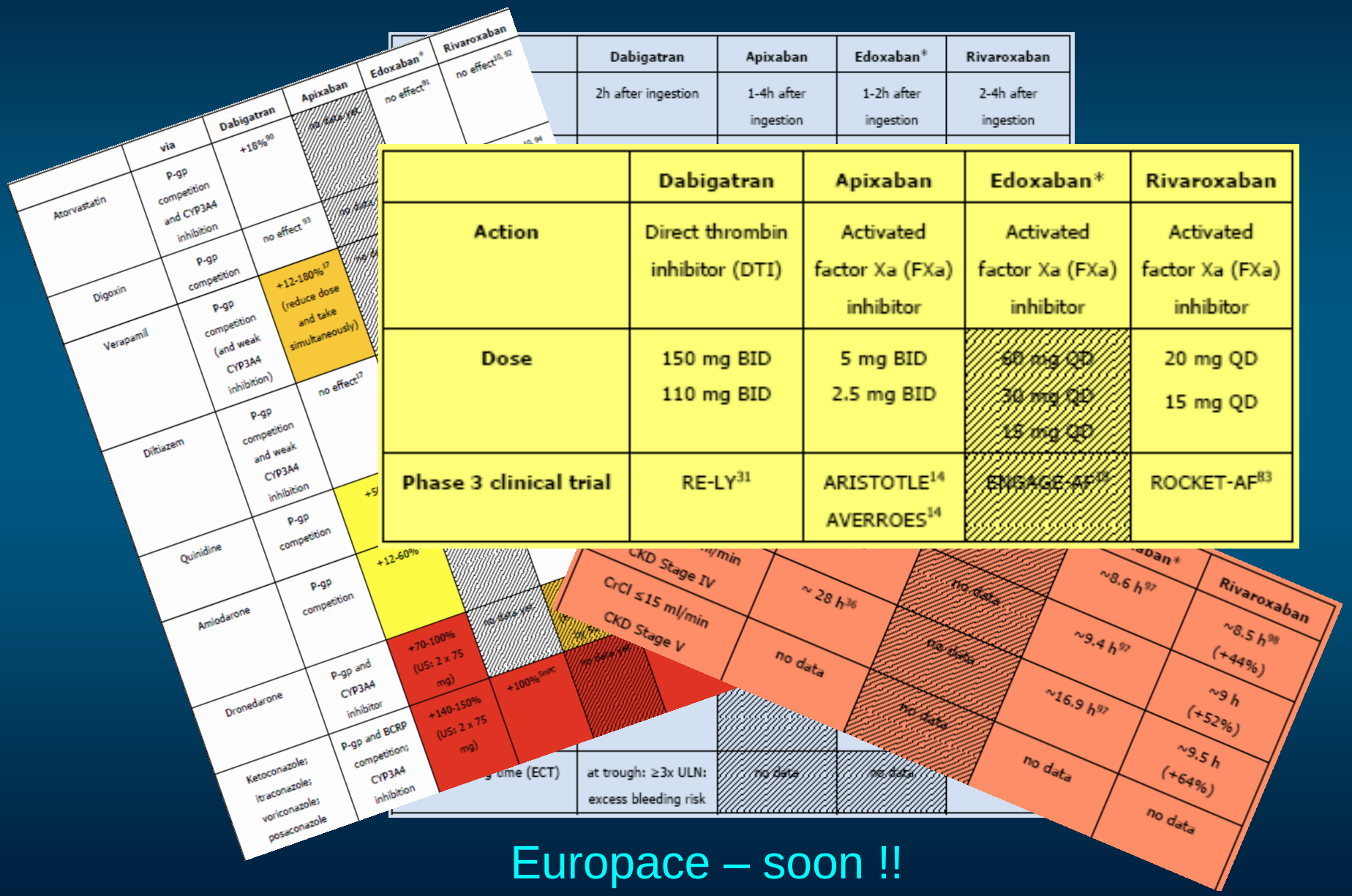
Contraindications include:

- PgP inhibitors: quinidine, dronedarone, protease inhibitors azole antifungals
- High bleeding risk

BID = twice daily; CrCl = creatinine clearance; NYHA = New York Heart Association

Adapted from: Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

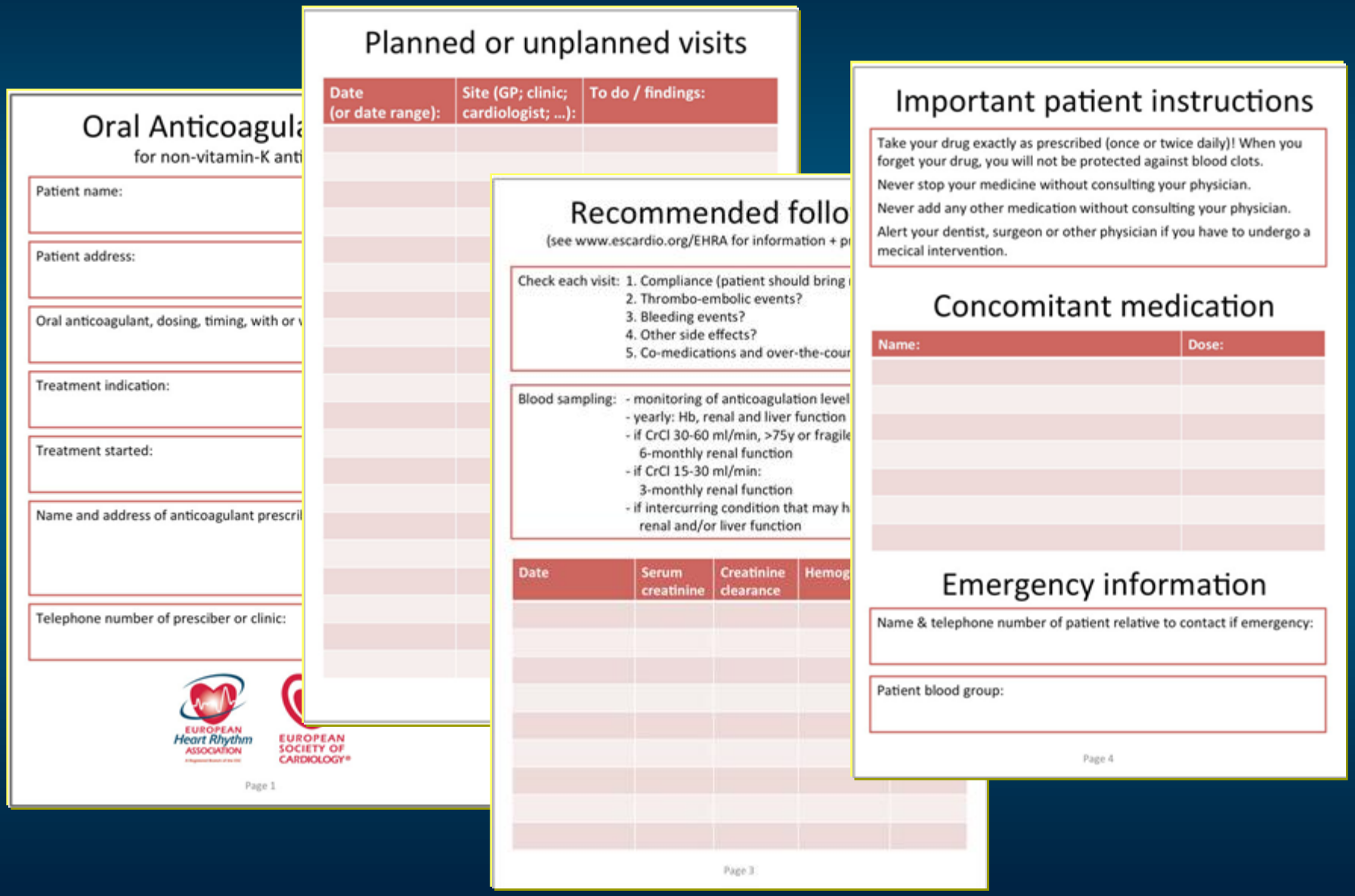
EHRA AF OAC Practical Guide



	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Action	Direct thrombin inhibitor (DTI)	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	60 mg QD 30 mg QD 15 mg QD	20 mg QD 15 mg QD
Phase 3 clinical trial	RE-LY[31]	ARISTOTLE[14] AVERROES[14]	ENGAGE-AF[84]	ROCKET-AF[83]

Europace – soon !!

EHRA AF OAC Follow-Up Card



Oral Anticoagula

for non-vitamin-K anti

Patient name:

Patient address:

Oral anticoagulant, dosing, timing, with or

Treatment indication:

Treatment started:

Name and address of anticoagulant prescri

Telephone number of presciber or clinic:

EUROPEAN Heart Rhythm ASSOCIATION

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Page 1

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; ...):	To do / findings:

Recommended follo

(see www.escardio.org/EHRA for information + p

Check each visit: 1. Compliance (patient should bring
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-cour

Blood sampling: - monitoring of anticoagulation level
- yearly: Hb, renal and liver function
- if CrCl 30-60 ml/min, >75y or fragile
6-monthly renal function
- if CrCl 15-30 ml/min:
3-monthly renal function
- if intercurring condition that may h
renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemog

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Important patient instructions

Take your drug exactly as prescribed (once or twice daily)! When you forget your drug, you will not be protected against blood clots.

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician.

Alert your dentist, surgeon or other physician if you have to undergo a mecical intervention.

Concomitant medication

Name:	Dose:

Emergency information

Name & telephone number of patient relative to contact if emergency:

Patient blood group:

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