Management of atrial fibrillation

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Antithrombotic therapy in atrial fibrillation

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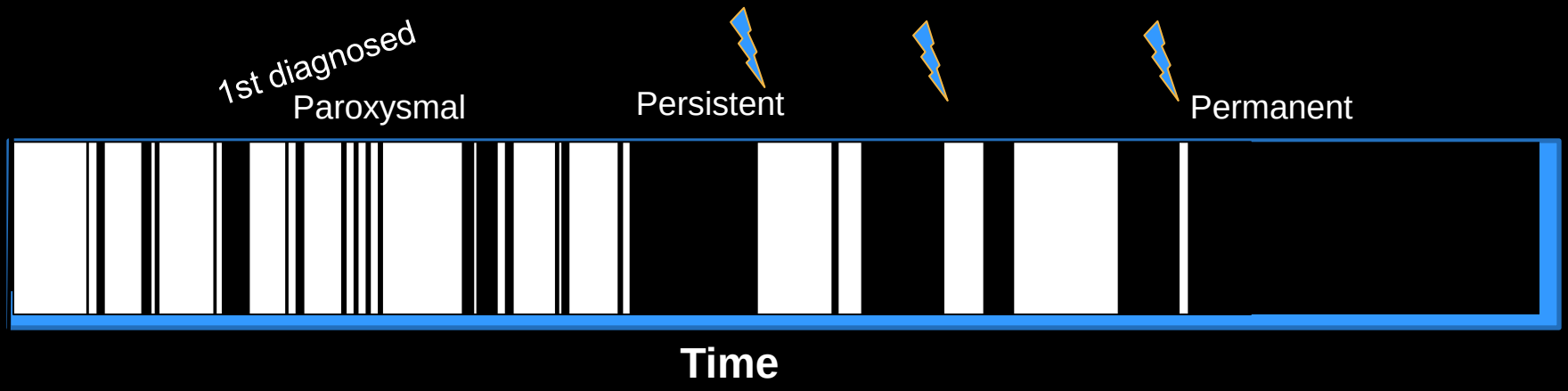
AF has serious consequences

- Independent risk factor for stroke
  - Approximately fivefold increased risk[1]
  - 1 in 6 strokes occur in patients with AF[2]
  - AF-related strokes are typically more severe than strokes due to other aetiologies[3,4]
  - Stroke risk is unaltered even in patients with asymptomatic or intermittent AF[5]

1. Wolf PA *et al*. *Stroke* 1991;22:983–988; 2. Fuster V *et al*. *Circulation* 2006;114:e257–e354; 3. Lin HJ *et al*. *Stroke* 1996;27:1760–1764; 4. Jørgensen HS *et al*. *Stroke* 1996;10:1765–1769; 5. Page RL *et al*. *Circulation* 2003;107:1141–1145; 6. Benjamin EJ *et al*. *Circulation* 1998;98:946–952; 7.Wang T *et al*. *Circulation* 2003;107:2920–2925

‘Natural’ time course of AF: AF is a chronically progressive disease

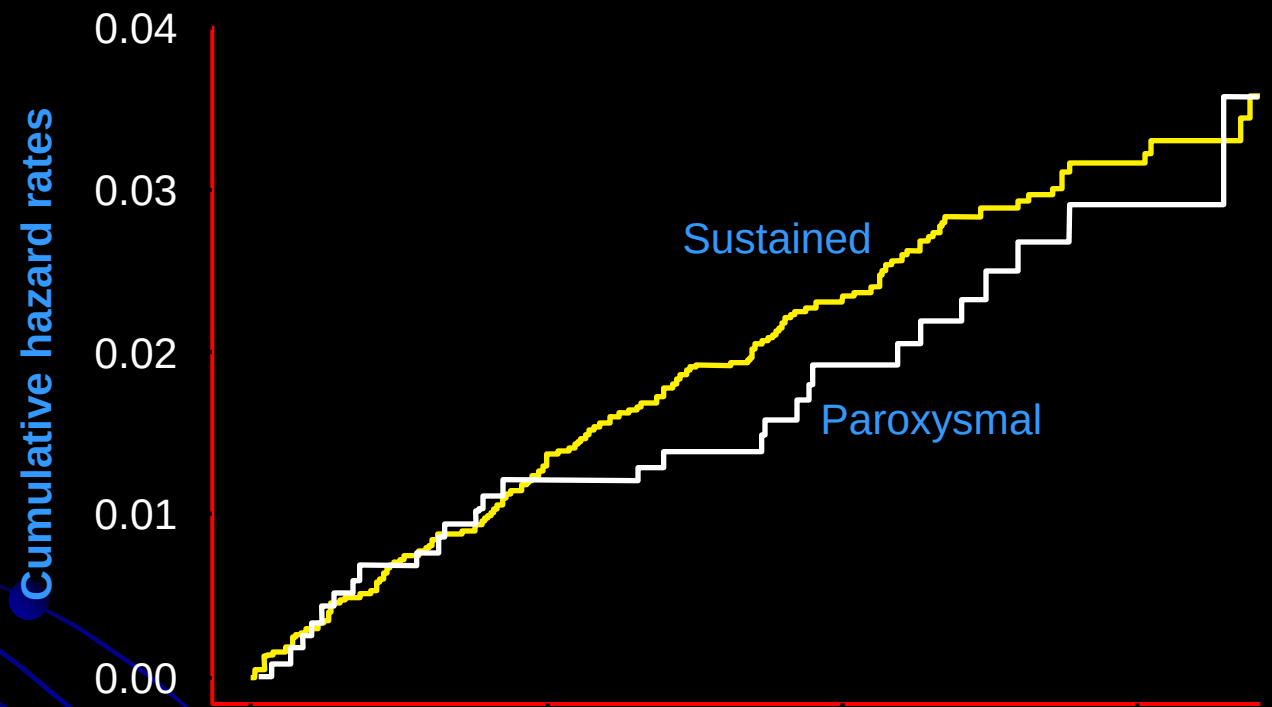


- Figure shows a typical chaotic pattern of time in AF (black) and time in sinus rhythm (white) over time
- Progress of AF occurs from undiagnosed to first diagnosed, paroxysmal, persistent, to permanent

Flashes indicate therapeutic interventions that influence the ‘natural’ time course of the arrhythmia, e.g. cardioversions

Kirchhof P *et al. Europace* 2007;9:1006–1023

Incidence of stroke or non-CNS systemic embolism according to type of AF



No. at risk				
Paroxysmal	1,199	1,121	862	304
Sustained	5,499	5,264	4,006	1,560

Patients with paroxysmal AF have similar risks of stroke and non-CNS systemic embolism as patients with sustained (permanent) AF

Hohnloser SH *et al. Am Coll Cardiol* 2007;50:2156–2161

Risk of stroke in AF

- Valvular AF = very high risk
  - Rheumatic mitral disease
  - Mechanical prosthetic valve
  - Post MV repair
- Nonvalvular AF = very broad spectrum

Risk factor	Score
CHF/ LV dysfunction	1
Hypertension	1
Age ≥ 75 yrs	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65-74	1
Sex (female)	1
Maximum score	**9**

CHA_2DS_2-VASc score

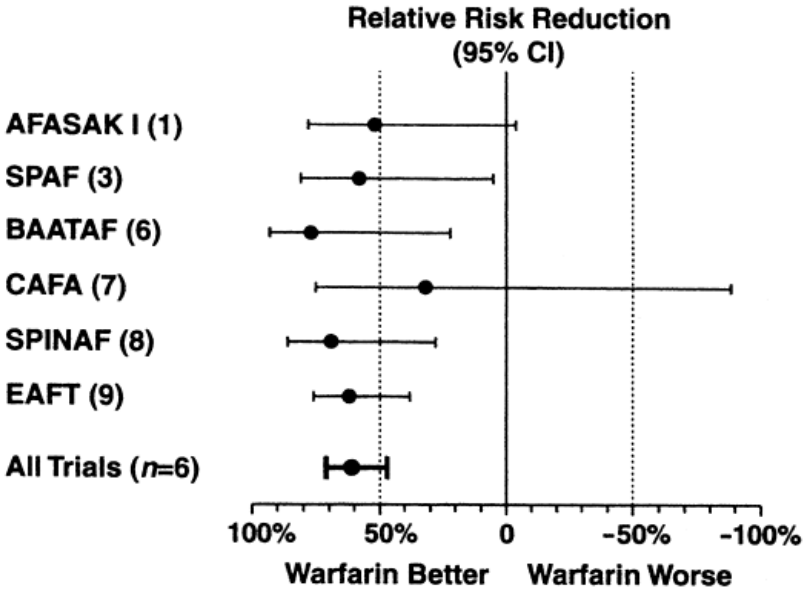
Risk factor	Score
Recent CHF	1
Hypertension	1
Age ≥ 75 yrs	1
Diabetes mellitus	1
History of stroke or TIA	2
Maximum score	**6**

$CHADS_2$ score

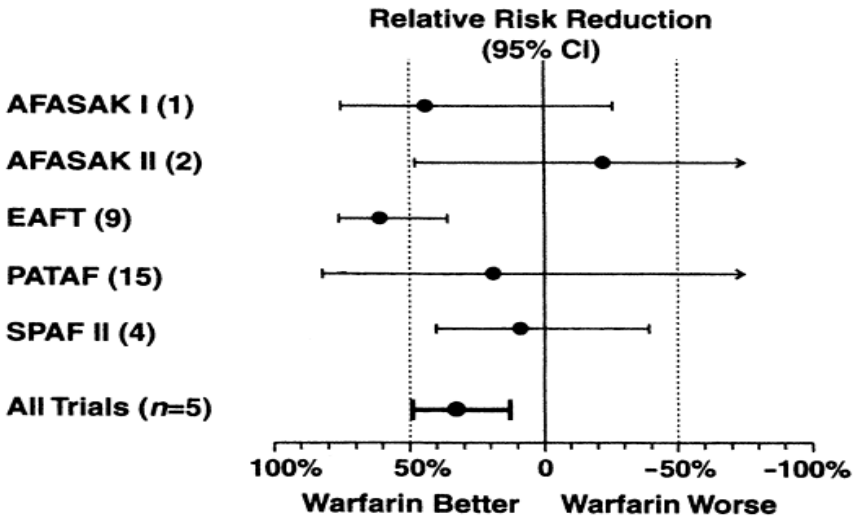
These should be combined with the "less validated risk factors"

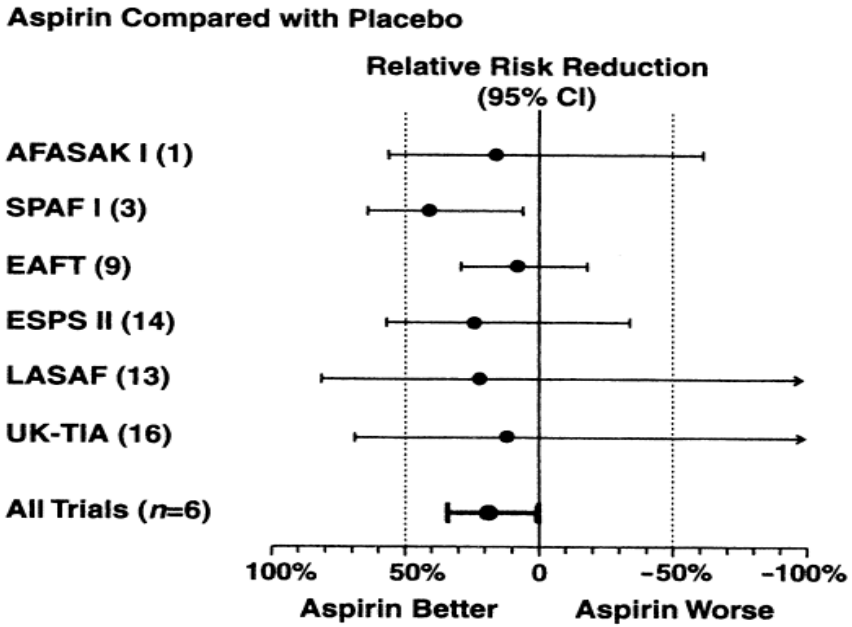
CHA_2DS_2-VASc score	Adjusted stroke rate (%/y)	$CHADS_2$ score	Adjusted stroke rate (%/y)
0	0%	0	1.9
1	1.3%	1	2.8
2	2.2%	2	4.0
3	3.2%	3	5.9
4	4.0%	4	8.5
5	6.7%	5	12.5
6	9.8%	6	18.2
7	9.6%		
8	6.7%		
9	15.2%		

The “Sweet Clover”



There is no question regarding efficacy of warfarin in prevention of stroke for patients with AF





Risk of bleeding: "HAS-BLED score"

HAS-BLED risk criteria		Score
Hypertension	✓	1
Abnormal renal or liver function (1 point each)		1 or 2
Stroke	✓	1
Bleeding		1
Labile INRs	✓	1
Elderly (e.g. age >65 yrs)	✓	1
Drugs or alcohol (1 point each)	✓	1 or 2

INR = international normalized ratio

HAS-BLED total score	N	Number of bleeds	Bleeds per 100 patient-yrs*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.5
6	2	0	0.0
7	0	–	–
8	0	–	–
9	0	–	–

*P value for trend = 0.007

Pisters R et al. Chest. 2010;138:1093–100; ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429

The net clinical benefit (NCB) of VKA treatment is higher in patients with a high bleeding risk

HAS-BLED score	NCB VKA vs no treatment (95% CI)				
	≤2	≥3		≤2	≥3
$CHADS_2$	CHA_2DS_2-VASc				
0	–0.02 (–0.09–0.06)	0.19 (–1.39–1.77)	0	–0.11 (–0.20—0.03)	–
1	0.84 (0.70–0.99)	0.56 (0.16–0.95)	1	–0.02 (–0.15–0.11)	0.25 (–0.86–1.36)
2–6	1.95 (1.70–2.20)	2.68 (2.33–3.04)	2–9	1.19 (1.07–1.32)	2.21 (1.93–2.50)

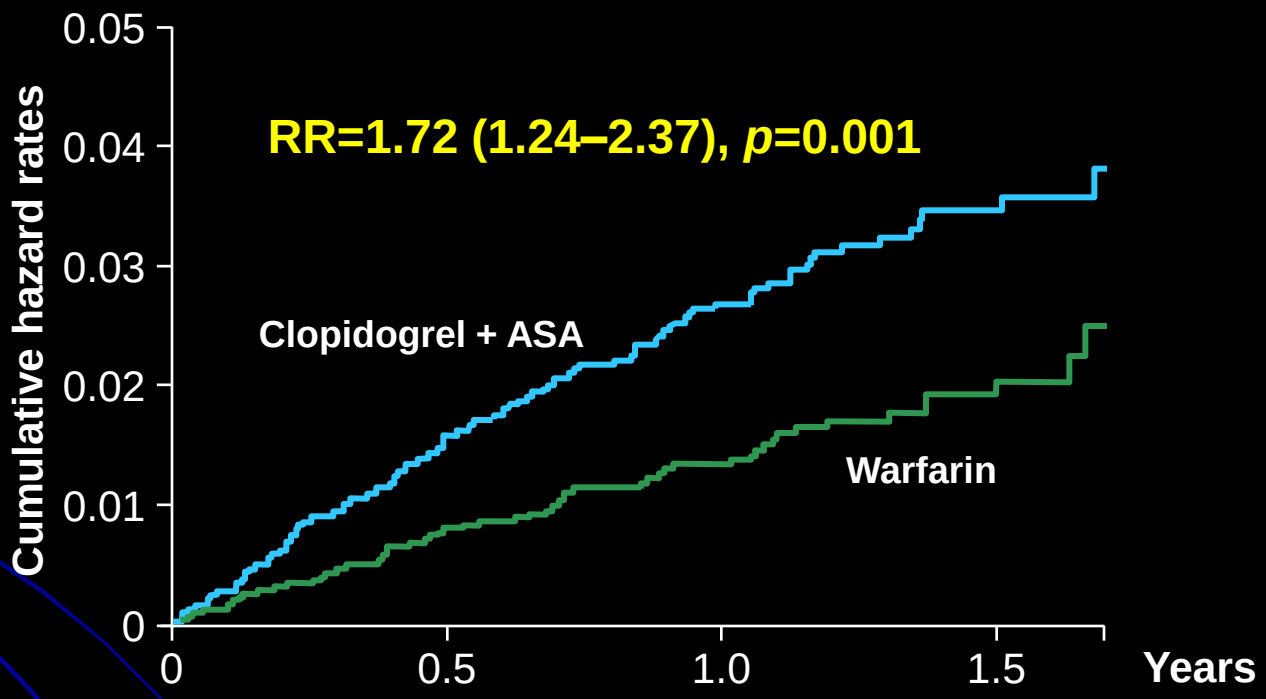
Values >0 favours treatment

- Negative NCB of OAC in 'truly low risk' patients (i.e. CHA_2DS_2-VASc=0)
- Significant positive NCB in patients with a $CHADS_2$ ≥1, and CHA_2DS_2-VASc ≥2
- The NCB with VKA was higher in patients with a HAS-BLED ≥3

Olesen JB *et al. Thromb Haemost* 2011;106

ACTIVE W: VKA is more effective than dual antiplatelet therapy

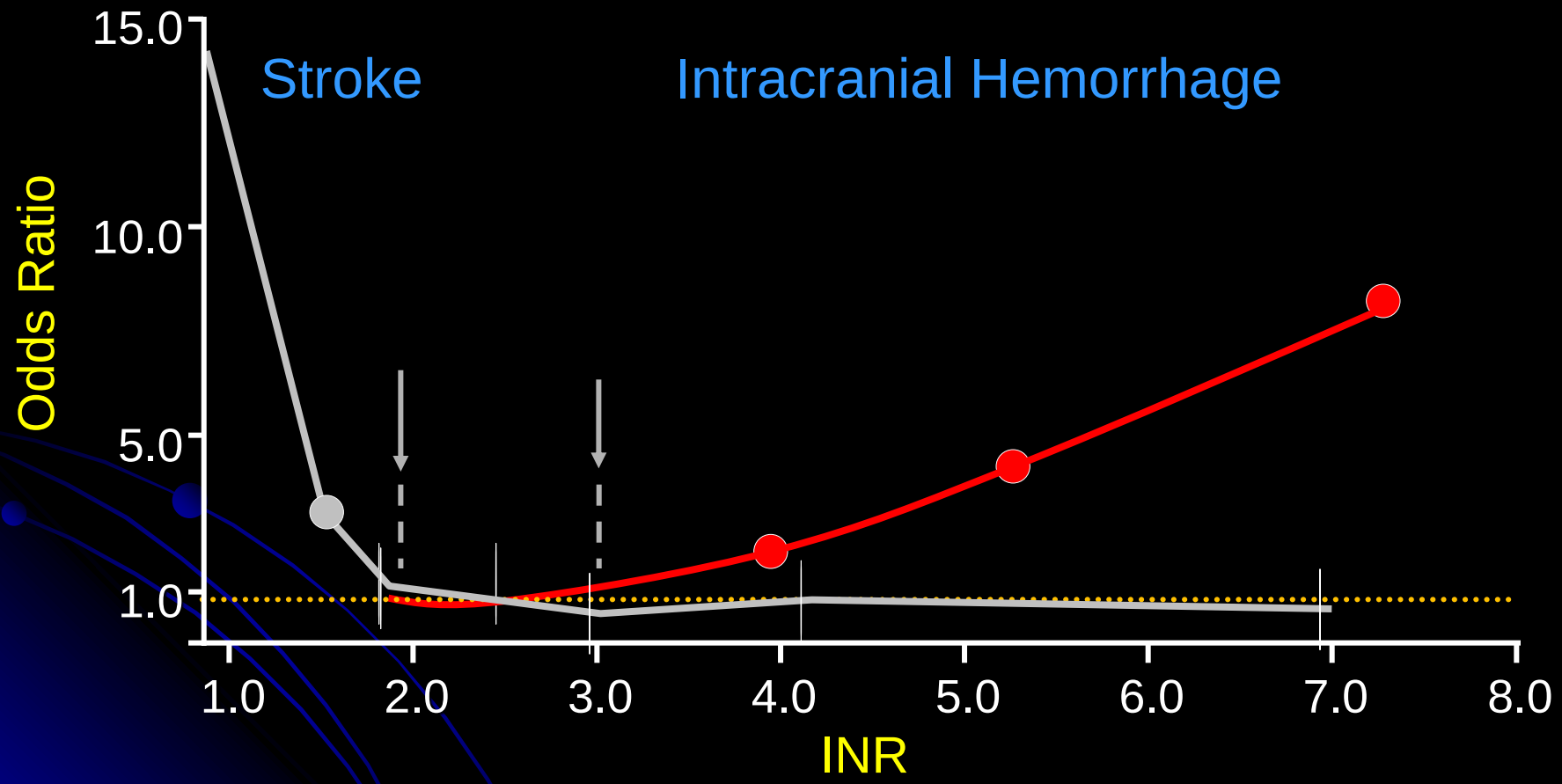
Cumulative risk of stroke



	Number at risk			
Clopidogrel + ASA	3,335	3,168	2,419	941
Oral anticoagulation therapy	3,371	3,232	2,466	930

Connolly S *et al*, 2006.

Therapeutic Range for Warfarin



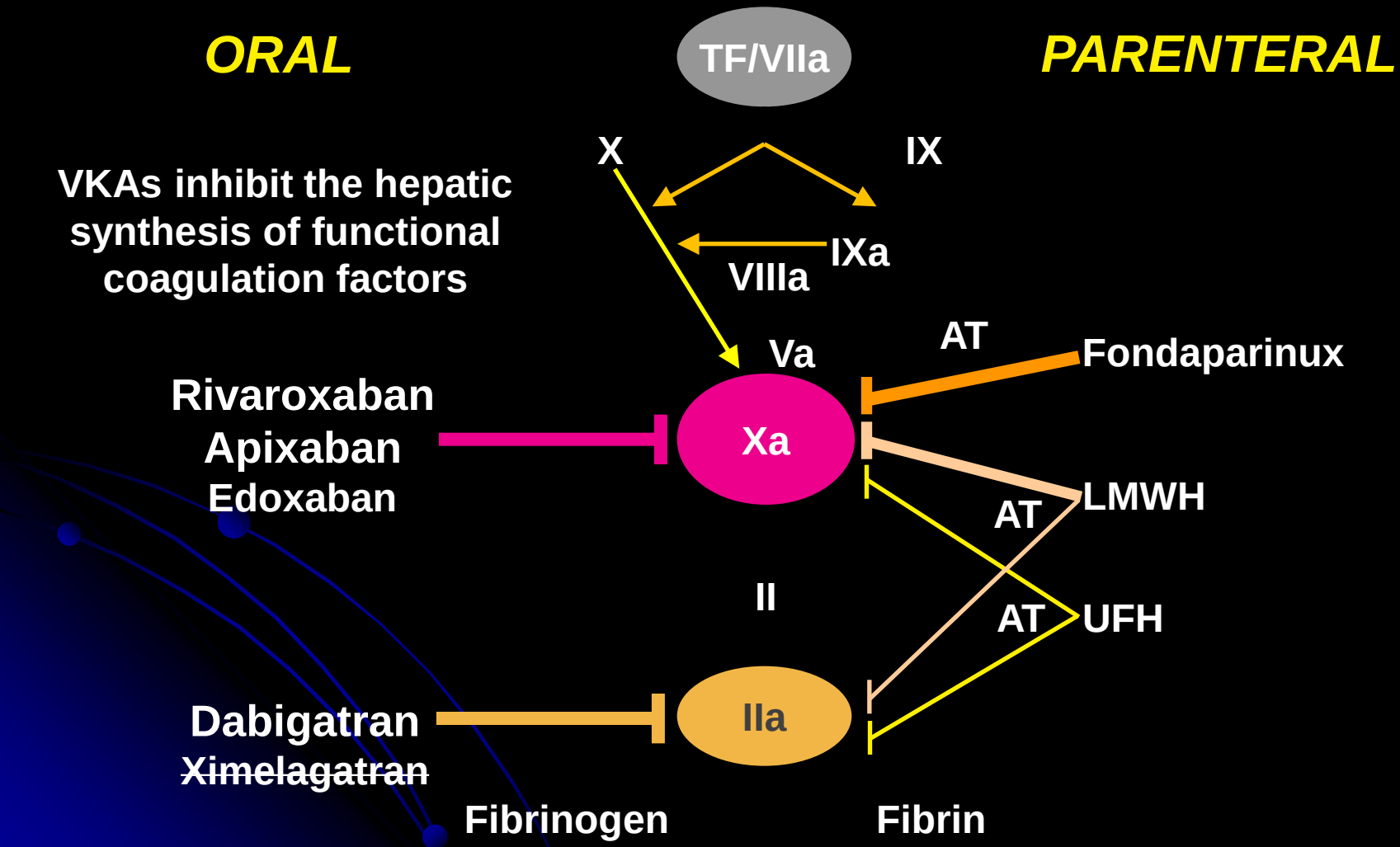
Fuster et al. *J Am Coll Cardiol*. 2001;38:1231-1266.

Problems with Warfarin

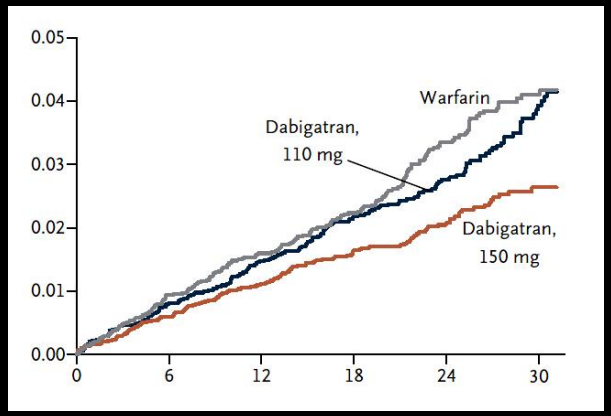
- Delayed onset/offset
- Unpredictable dose response
- Narrow therapeutic range
- Drug–drug, drug–food interactions
- Problematic monitoring
- High bleeding rate
- Slow reversibility


SOUVENIRS

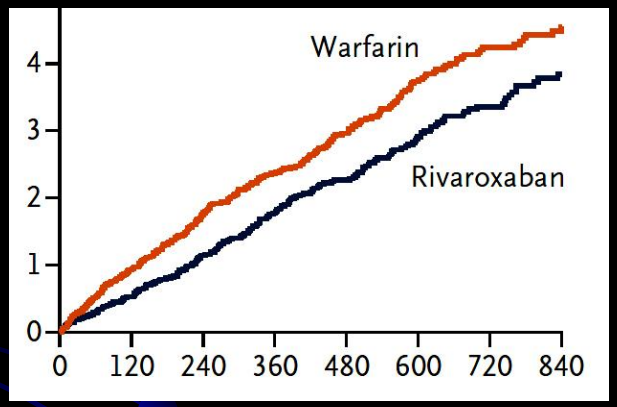
Targets for anticoagulants



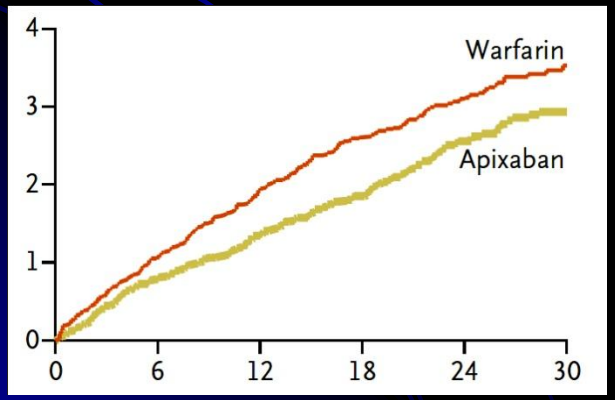
Adapted from 1. Weitz JI *et al. J Thromb Haemost* 2005;3:1843–1853; 2. Weitz JI *et al. Chest* 2008;133:234–256



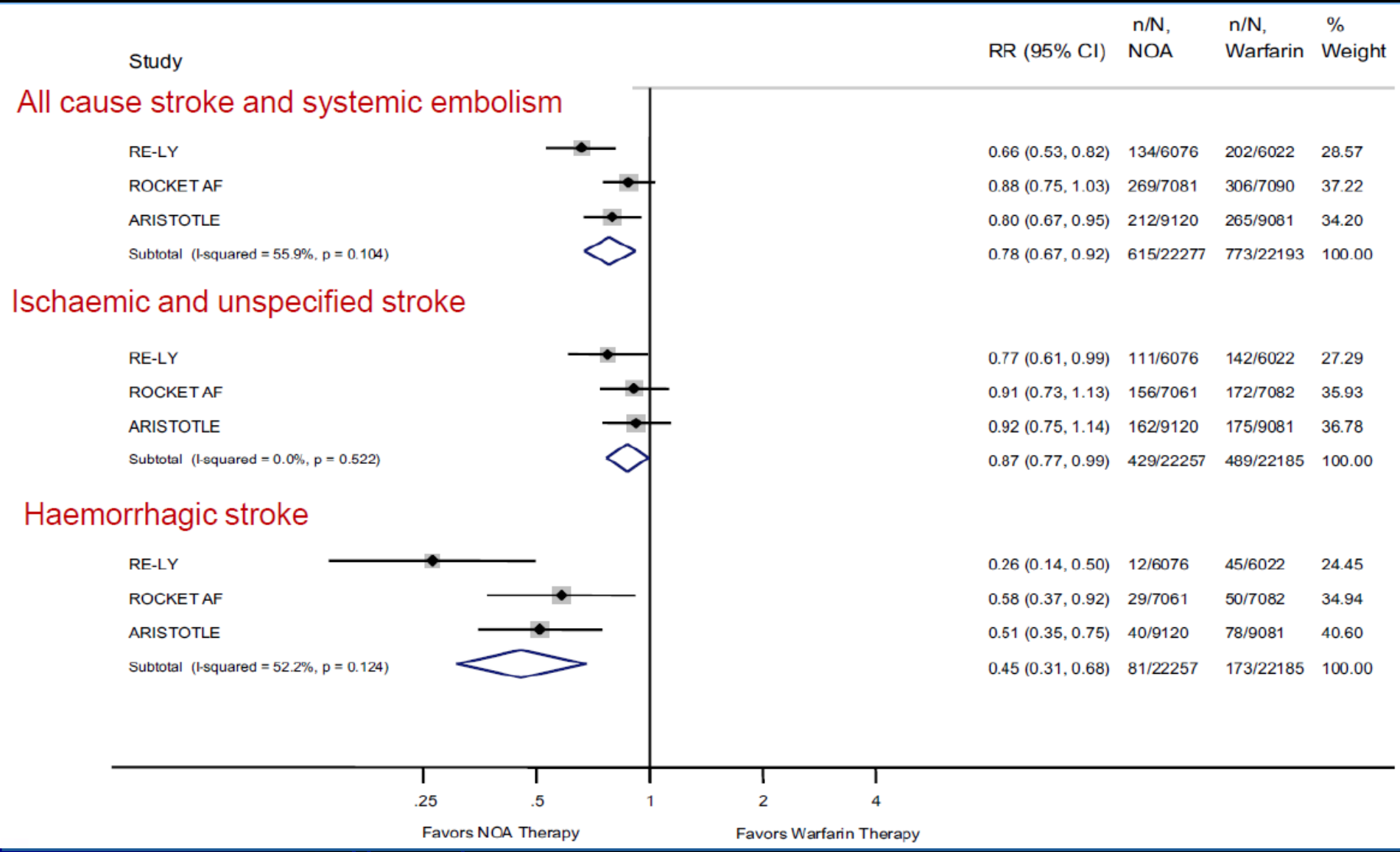
RE-LY study: Dabigatran VS Warfarin



ROCKET AF: Rivaroxaban VS Warfarin



ARISTOTLE: Apixaban VS Warfarin



Miller et al. AJC

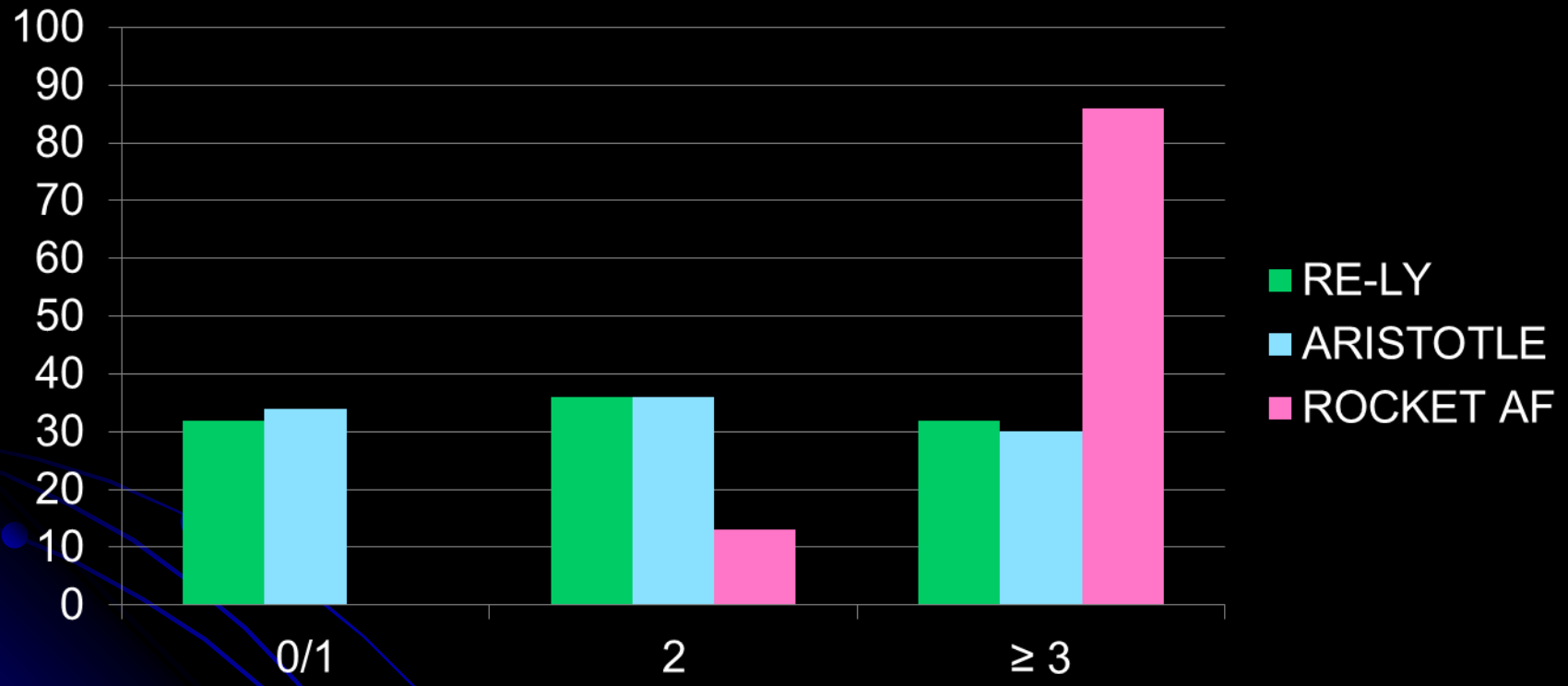
Comparison of the pharmacological characteristics of newer OACs

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Oral bioavailability	6.5%	**80–100%***	~66%	50%
Plasma protein binding	34–35%	92–95%	87%	40–59%
Dosing (for SPAF indication)	Fixed, twice daily	**Fixed, once daily**	Fixed, twice daily	Fixed, once daily
Prodrug	Yes	**No**	No	No
Half-life (h)	12–14	5–9 (young healthy) 11–13 (elderly)	8–13	9–11
T_{max} (h)	~6	2–4	1–3	1–2
Routine coagulation monitoring	No	No	No	No

*15–20 mg to be taken with food

Eriksson BI *et al*, 2011; Frost *et al,* 2007; Kubitza D *et al,* 2005; Kubitza D *et al,* 2005; Ogata K *et al,* 2010; Stangier *et al,* 2005; Raghavan N *et al,* 2009; Xarelto SmPC 2011; Xarelto PI 2011; Pradaxa SmPC 2011; Eliquis SmPC 2011; Dabigatran PI; ROCKET AF Investigators 2010; Lopes *et al*, 2010; Ruff *et al,* 2010.

$CHADS_2$ Distribution Across Trials



- Dabigatran and apixaban: evaluated across a spectrum of stroke risk categories
- Rivaroxaban: evaluated in patients at high risk of stroke

Connolly *N Engl J Med* 2009;361:1139; Patel *N Engl J Med* 2011365:883; Granger *N Engl J Med* 2011;365:981; Ruff *Am Heart J* 2010;160:635

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

Stroke

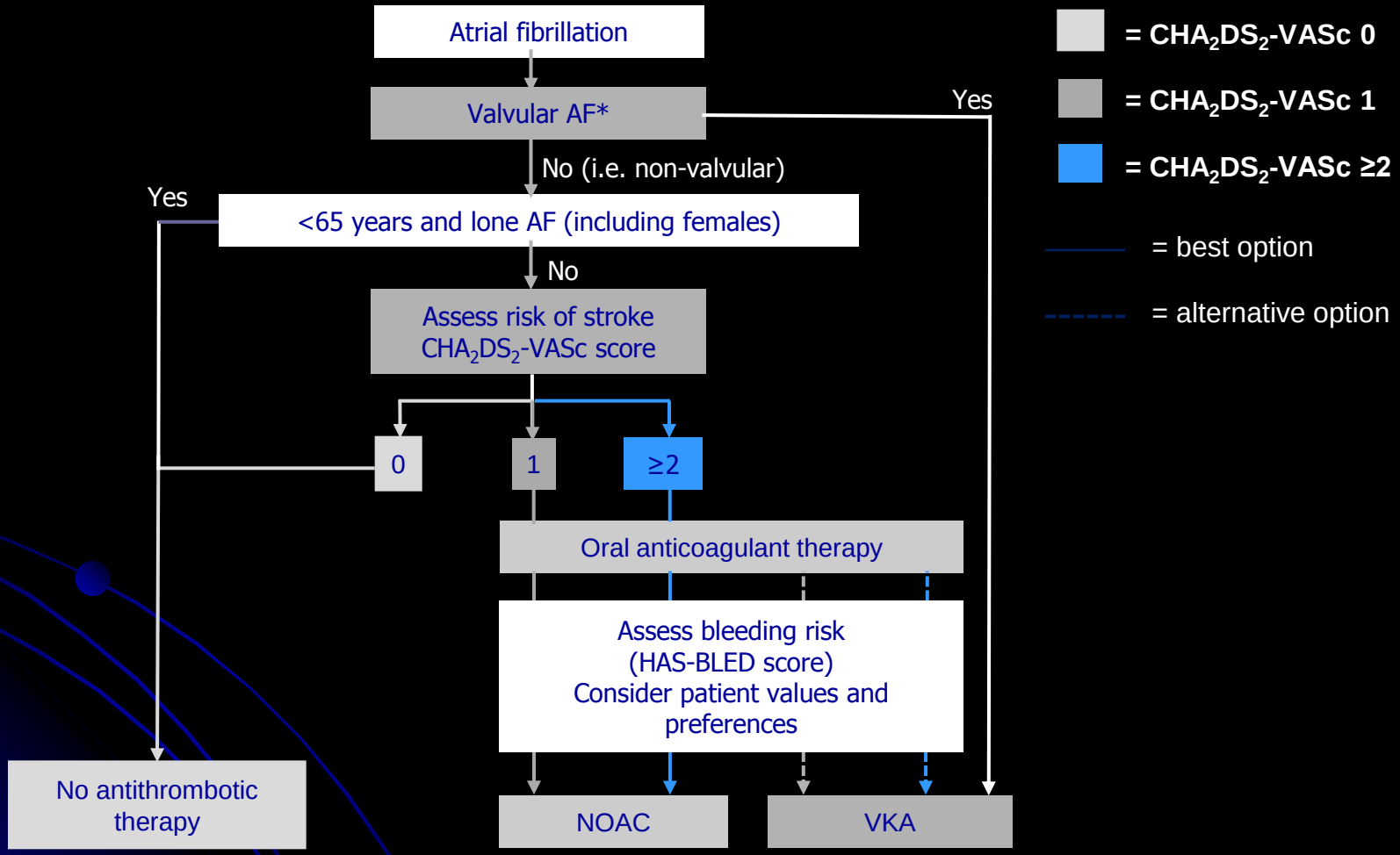
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation : A Science Advisory for Healthcare Professionals From the American Heart Association/American Stroke Association

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

ESC 2012 focused update: choice of anticoagulant



*Includes rheumatic valvular disease and prosthetic valves; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist; Camm AJ et al. Eur Heart J 2012;33:2719–47

Recommendation	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/undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **is recommended**	I	B
When OAC is recommended, one of the NOACs, either: in: • a direct thrombin inhibitor (dabigatran); or • an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **should be considered rather than adjusted-dose VKA** (INR 2–3) for most patients with nonvalvular AF, based on their net clinical benefit	IIa	A

*Pending approval; INR = international normalized ratio; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist; Camm AJ et al. Eur Heart J 2012;33:2719–47

2012 AHA/ASA science advisory: antithrombotic therapy in AF

- Agents indicated for prevention of stroke in patients with nonvalvular AF
  - Warfarin (Class I; Level of evidence A)
  - Dabigatran (Class I; Level of evidence B)
  - Apixaban (Class I; Level of evidence B)
  - Rivaroxaban (Class IIa; Level of evidence B)

	Existing AHA recommendation	New recommendation
Dabigatran	Useful alternative to warfarin for prevention of stroke/SE in patients with paroxysmal to permanent AF and risk factors for stroke/SE (without prosthetic heart valves, haemodynamically significant valve disease, CrCl <15 mL/min, or advanced liver disease)	150 mg BID: efficacious alternative to warfarin in patients with NVAF and ≥1 additional risk factor (and CrCl >30 mL/min)
Apixaban	None	5 mg BID: relatively safe and efficacious alternative to warfarin in patients with NVAF deemed appropriate for VKA therapy, with ≥1 additional risk factor and ≤1 of: age ≥80 years; weight ≥60 kg; serum creatinine ≥1.5 mg/dL
Rivaroxaban	None	20 mg/day: reasonable alternative to warfarin in patients with NVAF at moderate–high risk of stroke

	Dabigatran (RE-LY)[70, 71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Drug characteristics							
Mechanism	Oral direct thrombin inhibitor			Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor	
Bioavailability, %	6			60–80		50	
Time to peak levels, h	3			3		3	
Half-life, h	12–17			5–13		9–14	
Excretion	80% renal			2/3 liver, 1/3 renal		25% renal, 75% faecal	
Baseline patient characteristics							
Age, years	71.5 ± 8.7 (mean ± SD)			73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]	
Male sex, %	63.6			61.3		64.5	
$CHADS_2$ (mean)	2.1			3.5		2.1	
Outcomes (% per year)							
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban
	(*n* = 6022)	(*n* = 6076)	(*n* = 6015)	(*n* = 7133)	(*n* = 7131)	(*n* = 9081)	(*n* = 9120)
		(RR, 95% CI; *P* value)	(RR, 95% CI; *P* value)		(HR, 95% CI; *P* value)		(HR, 95% CI; *P* value)
Stroke/systemic embolism	1.69	1.11 (0.66, 0.53–0.82; *P* for superiority <0.001)	1.53 (0.91, 0.74–1.11; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12) (ITT)	1.6	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)
Ischaemic stroke	1.2	0.92 (0.76, 0.60–0.98; *P* = 0.03)	1.34 (1.11, 0.89–1.40; *P* = 0.35)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)

	Dabigatran (RE-LY)[70,71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* =0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)
Major bleeding	3.36	3.11 (0.93, 0.81–1.07; *P* = 0.31)	2.71 (0.80, 0.69–0.93; *P* = 0.003)	3.4	3.6 (*P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)
Intracranial bleeding	0.74	0.30 (0.40, 0.27–0.60; *P* <0.001)	0.23 (0.31, 0.20–0.47; *P* <0.001)	0.7	0.5 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92–1.25; *P* = 0.38)	2.51 (0.94, 0.80–1.10; *P* = 0.45)	–	–	–	–
Outcomes (% per year)							
Gastrointestinal bleeding	1.02	1.51 (1.50, 1.19–1.89; *P* <0.001)	1.12 (1.10, 0.86–1.41; *P* = 0.43)	2.2	3.2 (*P* <0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 096-1.75; *P* = 0.09)	1.1	0.9 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.2	1.9 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)
% Discontinuation at the end of follow-up	10.2	15.5	14.5	22.2	23.7	27.5	25.3
% Discontinuation/year	5.1	7.8	7.3	11.7	12.5	15.3	14.1

Interesting issues from EHRA

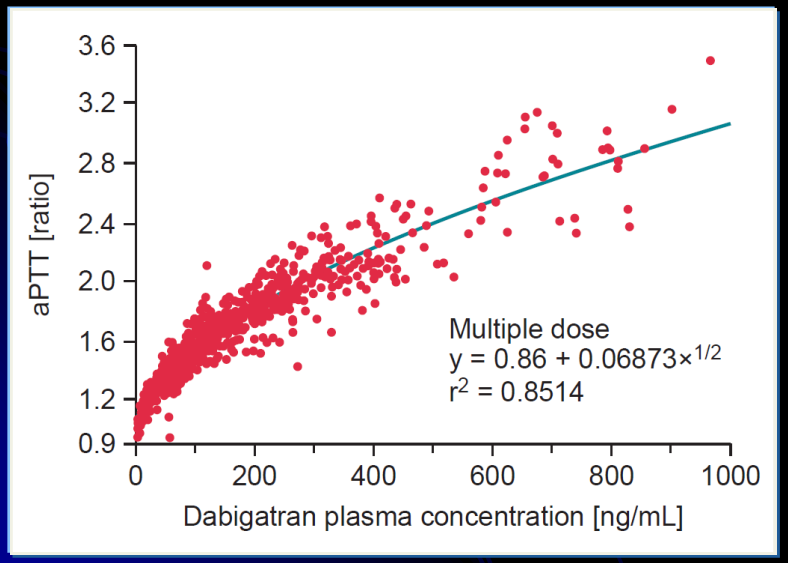
- Measuring of anticoagulant effect
- Drug-drug interaction
- Switching between (N)OAC
- Management of bleeding

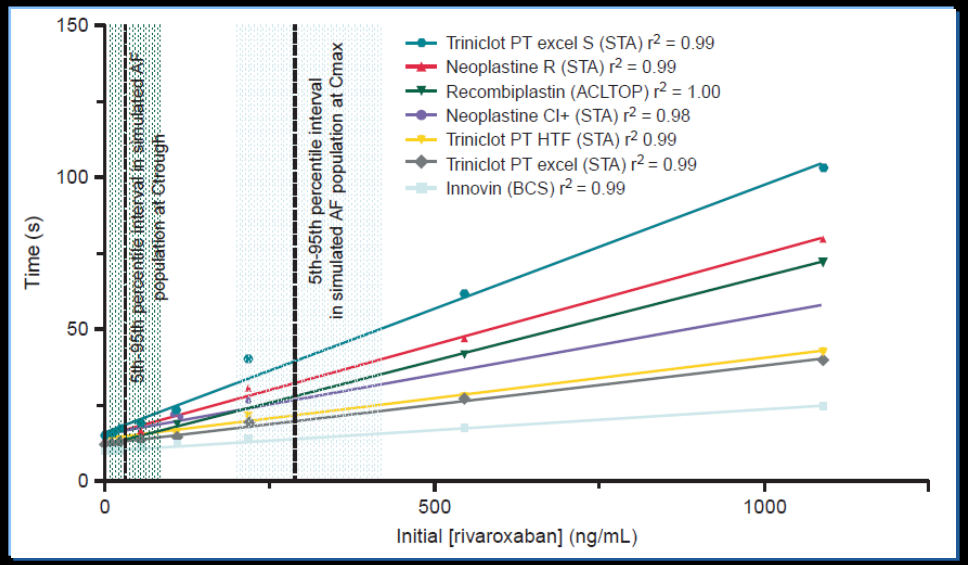
Coagulation assay for NOAC

Dabigatran: aPTT >2UNL 12-24 hrs after = high bleeding risk

Xa inhibitor: PT, lots of variation, Do not use INR

If coagulogram, do it after 24 hrs of last dose

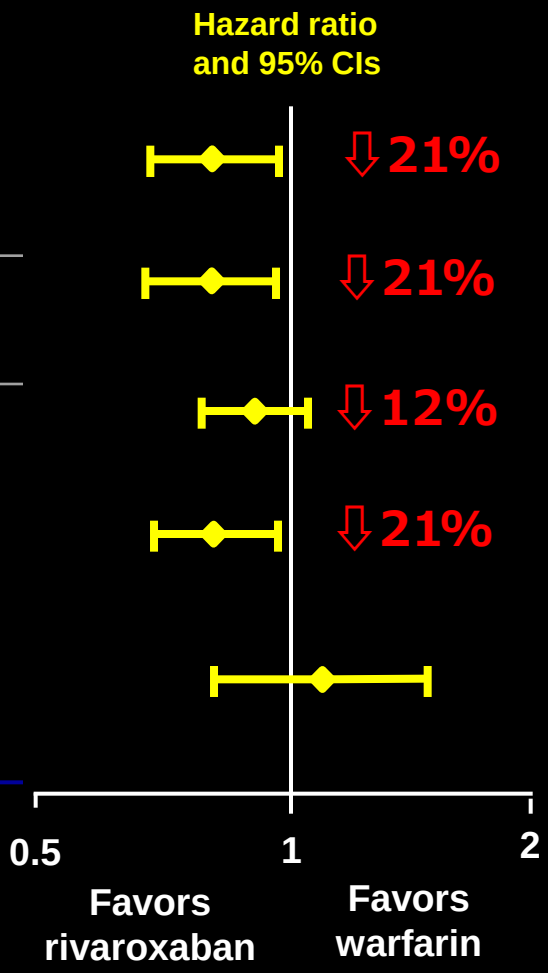




	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Amiodarone	P-gp competition	+12-60%[45]	no data yet	no effect[40]	minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (US: 2 x 75 mg)	no data yet	+85% (Reduce dose by 50%)*	no data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg)	+100%[Smith]	no data yet	up to +160%[42]
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15-20%	no data yet	no data yet	+30-54%[42, 46]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	no data yet	Strong increase[Smith]	no data yet	up to +153%[41]
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%[47]	-54%[Smith]	-35%	up to -50%

ROCKET AF – Primary Efficacy Endpoint On- and Off-Treatment

	Rivaroxaban n/N (% per year)	Warfarin n/N (% per year)	Hazard ratio (95% CI)	*p*-value Non-inf.	*p*-value Sup.
Per-protocol, as-treated	**188/6958 (1.7)**	**241/7004 (2.2)**	**0.79 (0.66,0.96)**	**<0.001**	
Safety, as-treated	**189/7061 (1.7)**	**243 /7082 (2.2)**	**0.79 (0.65,0.95)**		**0.02**
ITT	**269/7081 (2.1)**	**306/7090 (2.4)**	**0.88 (0.75,1.03)**	**<0.001**	**0.12**
ITT, during treatment	188 (1.7)	240 (2.2)	0.79 (0.66,0.96)		0.02
ITT, after discontunua-tion	81 (4.7)	66 (4.3)	1.10 (0.79,1.52)		0.58



Primary efficacy endpoint: stroke or systemic embolism
ITT during treatment, after discontinuation: *post hoc* analyses

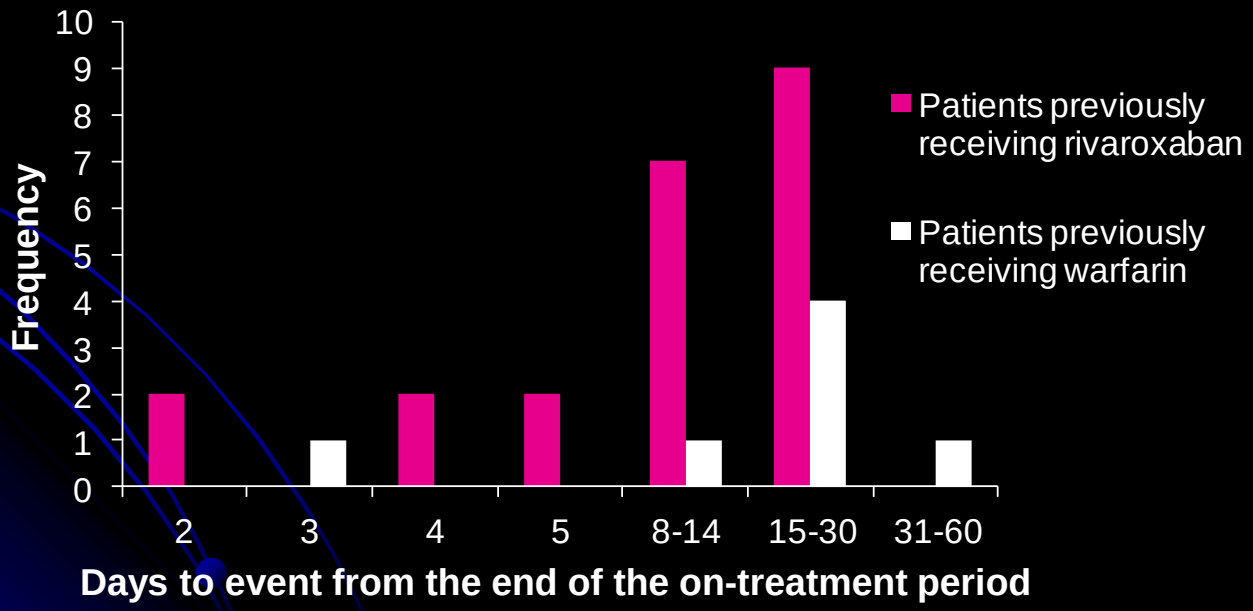
Intention-to-treat (ITT) population: all patients randomized (N=14,264)

Patel *et al. NEJM* 2011, August 10th epub ahead of print

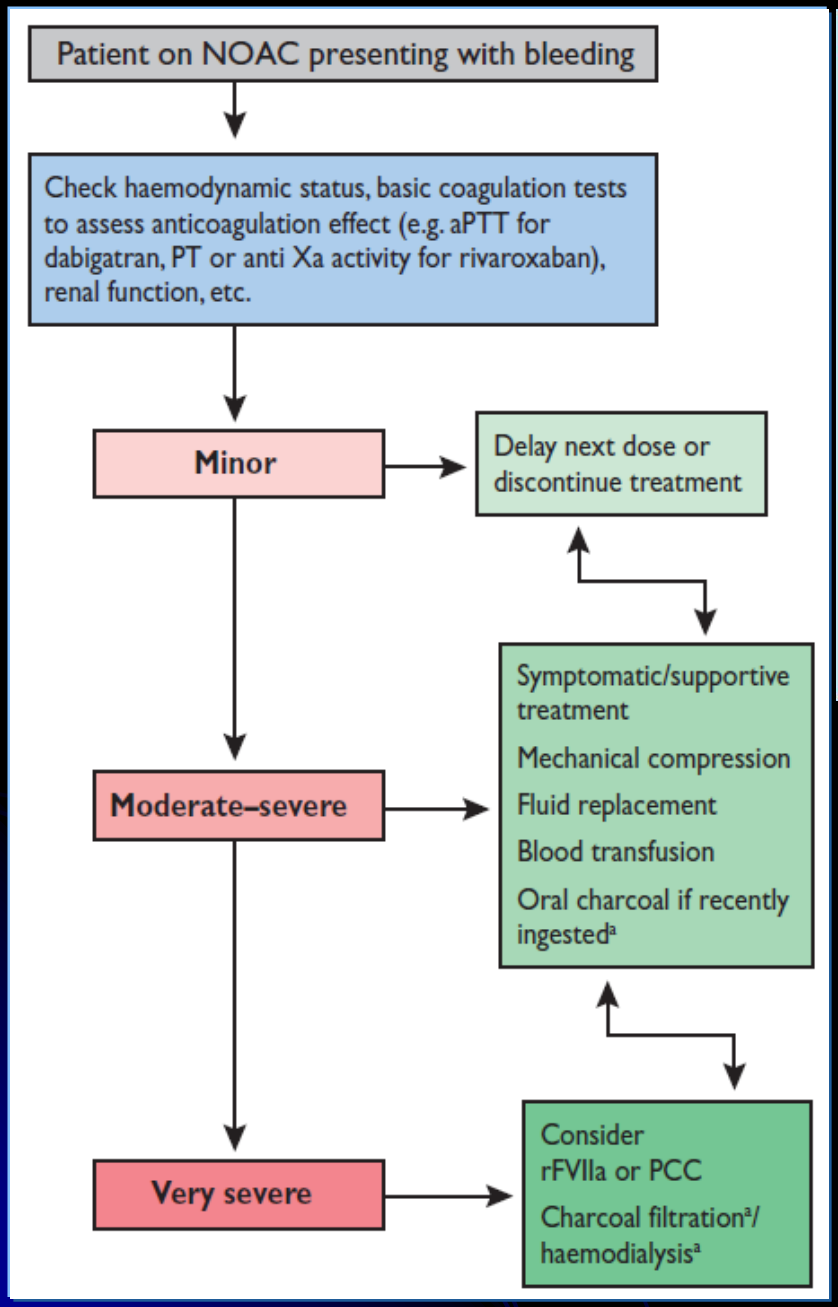
ROCKET AF – efficacy events at the end of the study in study completers

- Primary efficacy endpoint events during follow-up: 22 (patients previously receiving rivaroxaban) vs 7 (patients previously receiving warfarin), *p*=0.008
- **Median no. of days to reach INR 2–3 after last dose of study drug: 13 days (previously receiving rivaroxaban)**

Primary efficacy endpoint events within 60 days after last dose of study drug in patients completing study medication



Patel MR *et al. N Engl J Med* 2011;365:883–891



	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 ml/min: 24–36 h CrCl 30–50 ml/min: 36–48 h CrCl <30 ml/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: -65% after 4 h)[48] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max. 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

Conclusion:

Non life-threatening bleed: local management

Life-threatening bleed:

Dialysis and charcoal for Dabi

Consider PCC for all

Acute stroke: no fibrinolysis in most

Take home messages

- Patients with AF carry a risk for stroke.
- To determine how big the stroke risk is, various stratification schemes could be used.
- Please remember, we use the risk score for nonvalvular AF
- Anticoagulant > antiplatelet …… always

Thanks for your attention