新型抗凝血劑介紹

中國醫藥大學附設醫院

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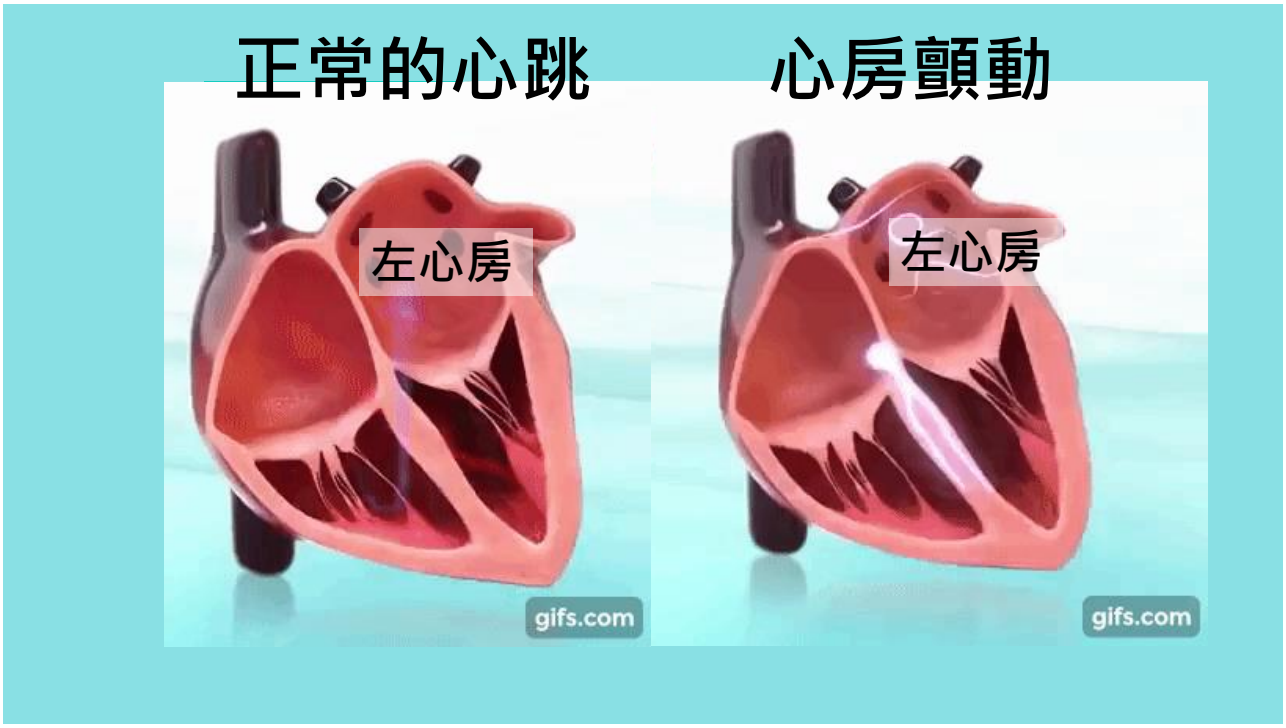
Outlines

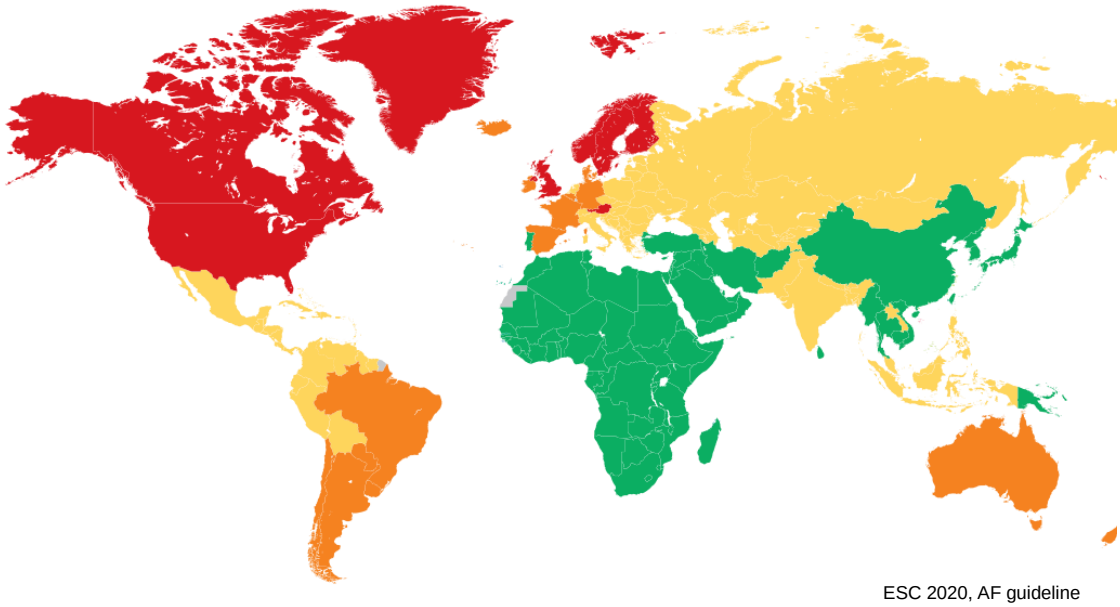
- Af introduction
- Coagulation pathway
- Comparison of NOACs
- Anti-coagulation in Af Pts with co-morbidity
- Summary
- Take home message

Outlines

- **Af introduction**

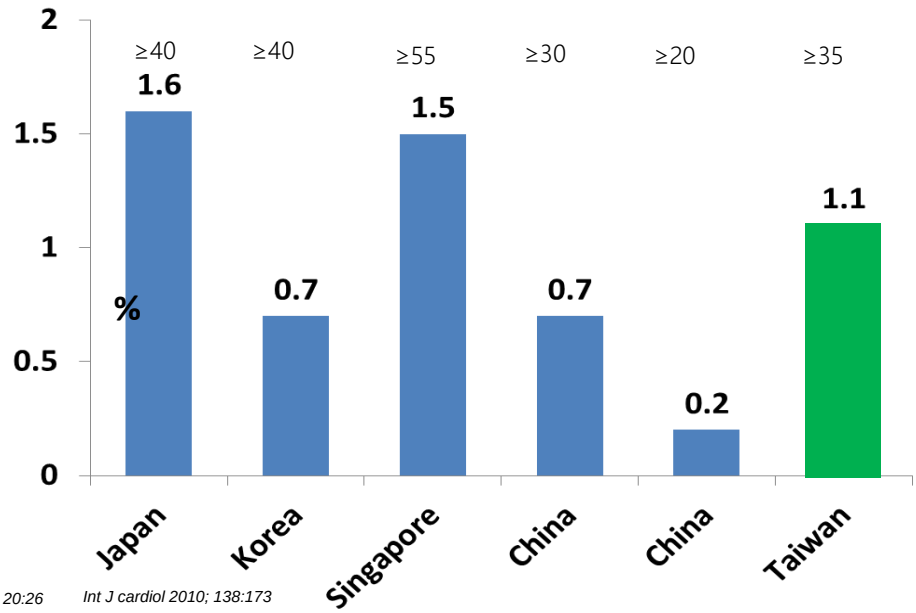


2016全球約4300萬人口罹病



ESC 2020, AF guideline

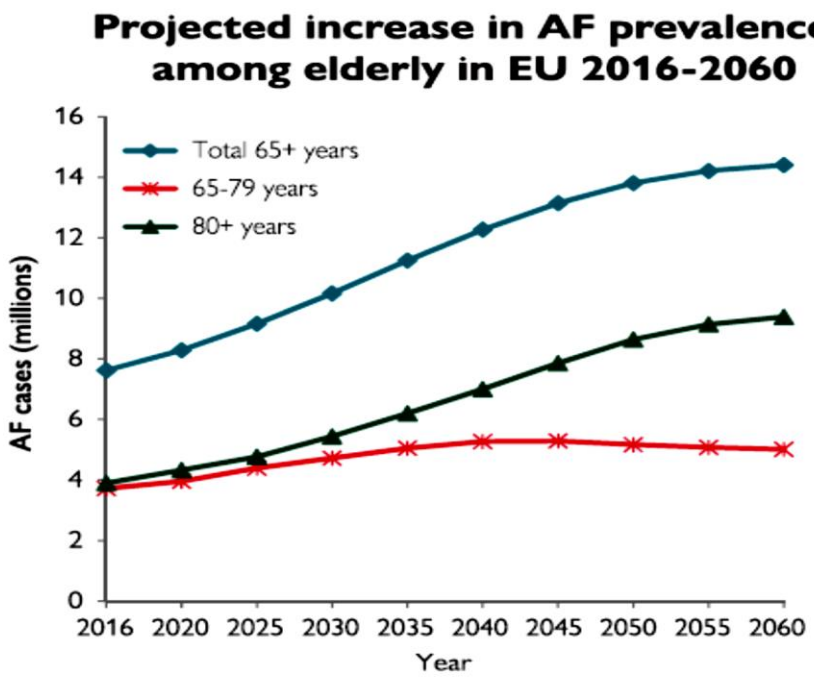
AF 亞洲盛行率



Circ J 2008; 72:909
***J** Korea Med Sci 2005; 20:26*
J Electrocardiol 2008; 41:94
Int J cardiol 2010; 138:173
J Epidemiol 2006; 18: 209

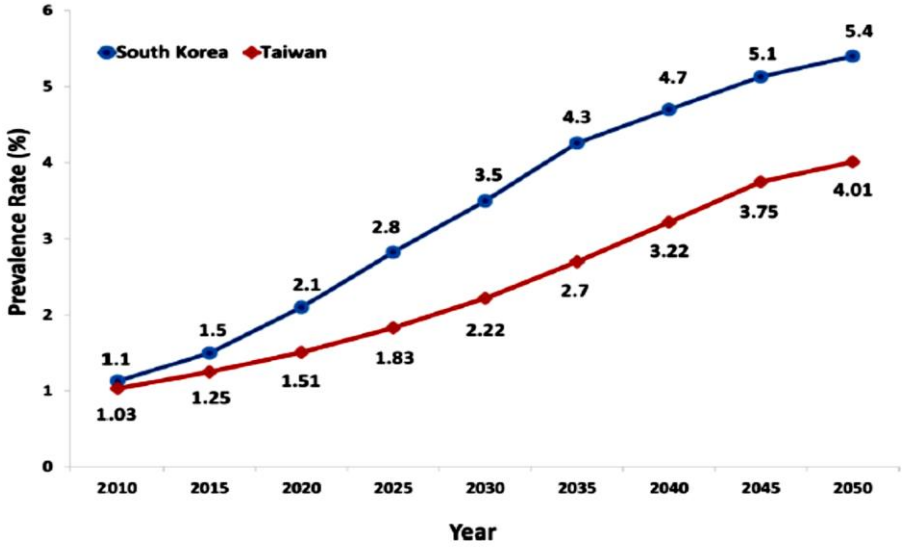
55歲時約每3人中一人就有心房顫動

of European ancestry

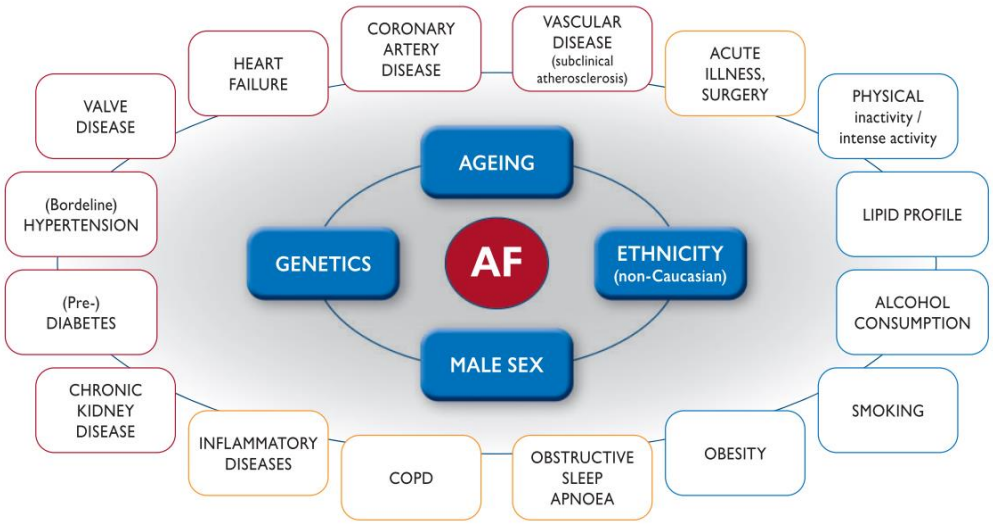


Projected prevalence of AF in Taiwan and South Korea.

Data used in the figure were adapted from the papers by Chao et al. and Kim et al

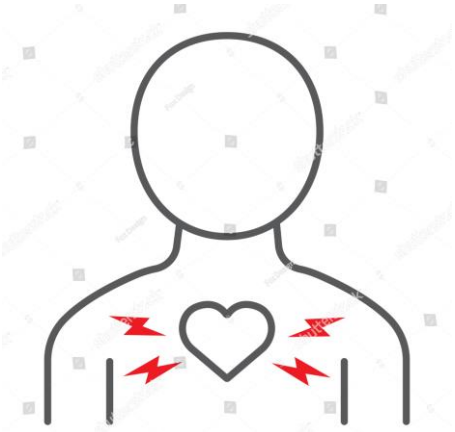


哪些人比較容易有心顫動

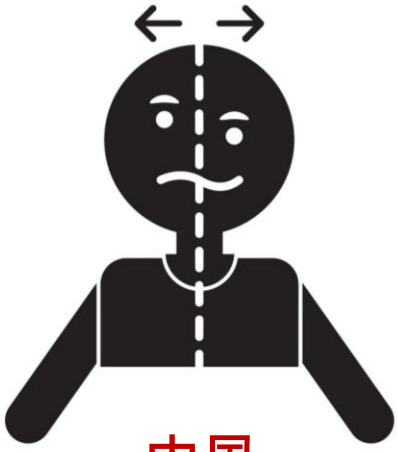


ESC 2020. AF guideline

心房顫動有什麼症狀

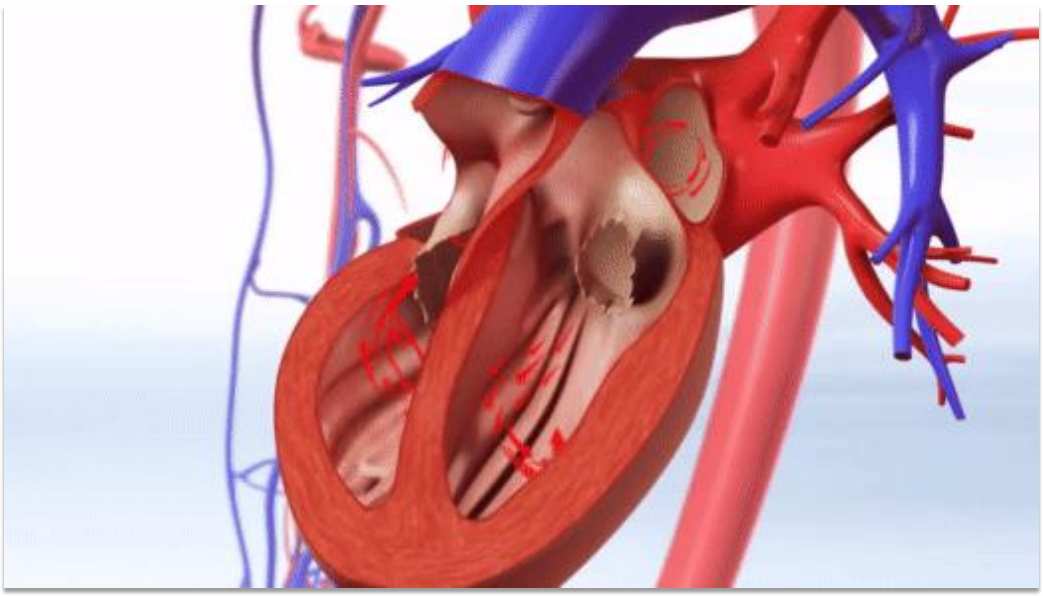


胸悶 心悸 喘



中風

心房顫動與中風



亞洲人腦出血機會是四倍

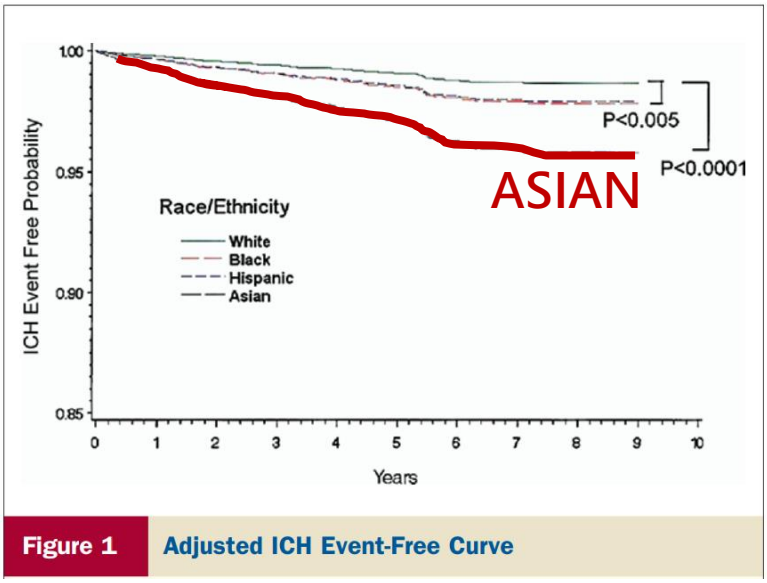
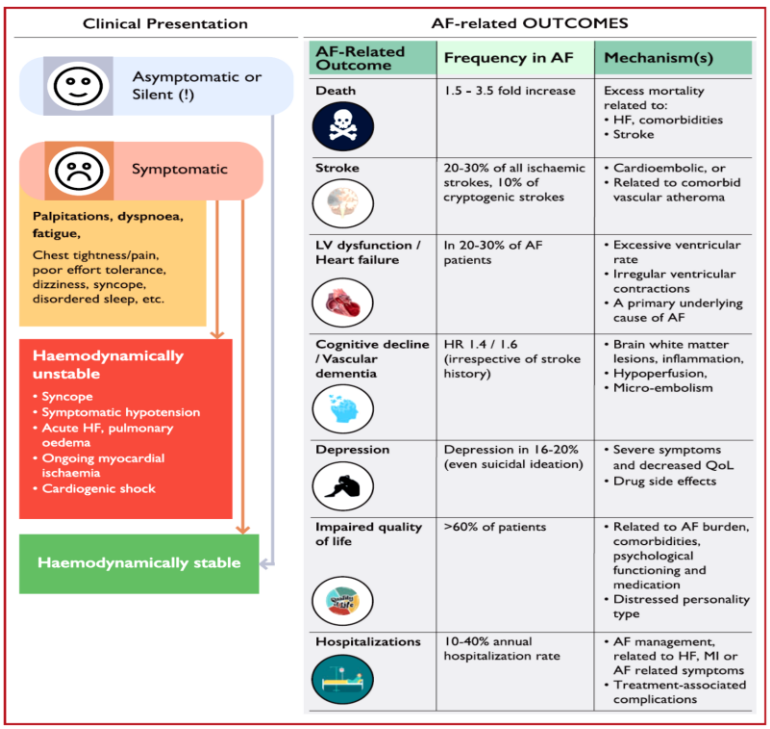


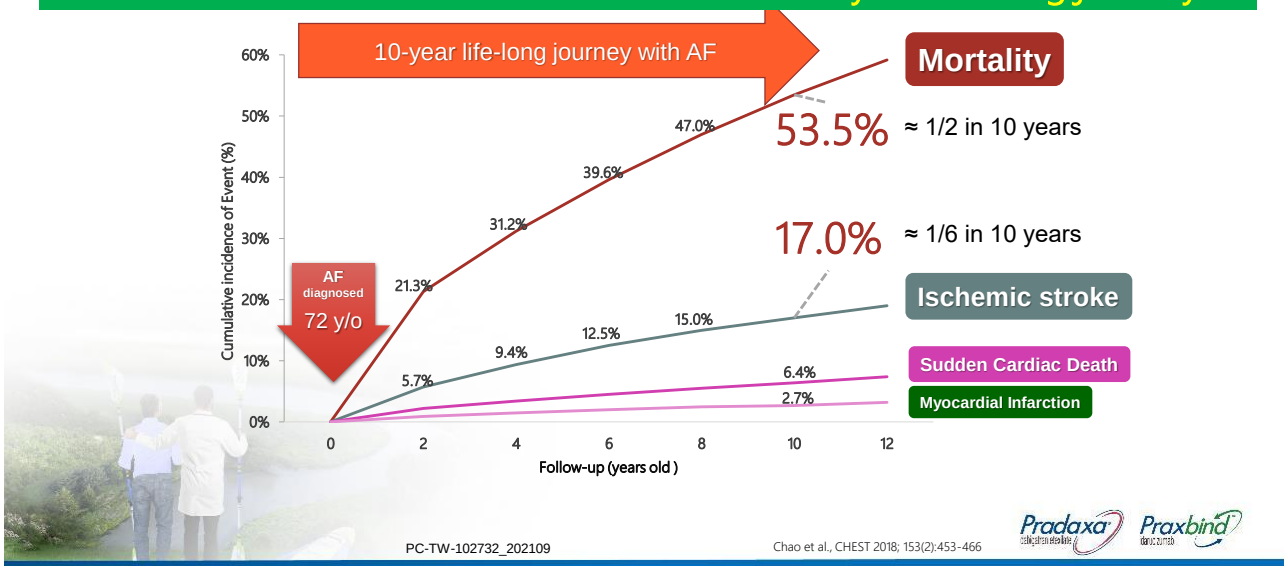
Figure 1 **Adjusted ICH Event-Free Curve**

Shen, A. Y.-J., Yao, J. F., Brar, S. S., Jorgensen, M. B., & Chen, W. (2007). *Racial/Ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients With Atrial Fibrillation. Journal of the American College of Cardiology, 50(4), 309 – 315.*



More than half of incident cases of AF were at the ages < 75 years old in Taiwan, with around *10 years* of life expectancy

How about the stroke and cardiac risks in this 10-year life-long journey ?



哪些人比較容易中風

Item	Points
Previous stroke TIA or systemic embolism	2
Age ≥75 years	2
Congestive heart failure*	1
Hypertension	1
Diabetes mellitus	1
Age 65–74 years	1
Female gender	1
Vascular disease**	1

Olesen JB *et al. BMJ* 2011;342:d124;
Camm AJ *et al. Eur Heart J* 2010;31:2369–2429

CHA_2DS_2-VASc score Risk factors and definitions		Points awarded	Comment
C	**Congestive heart failure** Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1	Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging[335]; HCM confers a high stroke risk[336] and OAC is beneficial for stroke reduction.[337]
H	**Hypertension** or on antihypertensive therapy	1	History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled BP today may not be well-controlled over time.[324] Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120-129/<80 mmHg.[338]
A	**Age 75 years or older**	2	Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards.[339] Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65-74 years and 2 points for age ≥75 years.
D	**Diabetes mellitus** Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1	Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thromboembolism[340]) and presence of diabetic target organ damage, e.g. retinopathy.[341] Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged <65 years with type 2 diabetes mellitus compared to patients with type 1 diabetes mellitus.[342]
S	**Stroke**Previous stroke, TIA, or thromboembolism	2	Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.[343–345]
V	**Vascular disease** Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1	Vascular disease (PAD or myocardial infarction) confers a 17-22% excess risk, particularly in Asian patients.[346–348] Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08-1.53).[349] Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke.[350]
A	**Age 65 – 74 years**	1	See above. Recent data from Asia suggest that the risk of stroke may rise from age 50-55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients.[351,352]
Sc	**Sex category (female)**	1	A stroke risk modifier rather than a risk factor.[353]
Maximum score		**9**	

CHA_2DS_2-VASc score Risk factors and definitions		Points awarded	Comment
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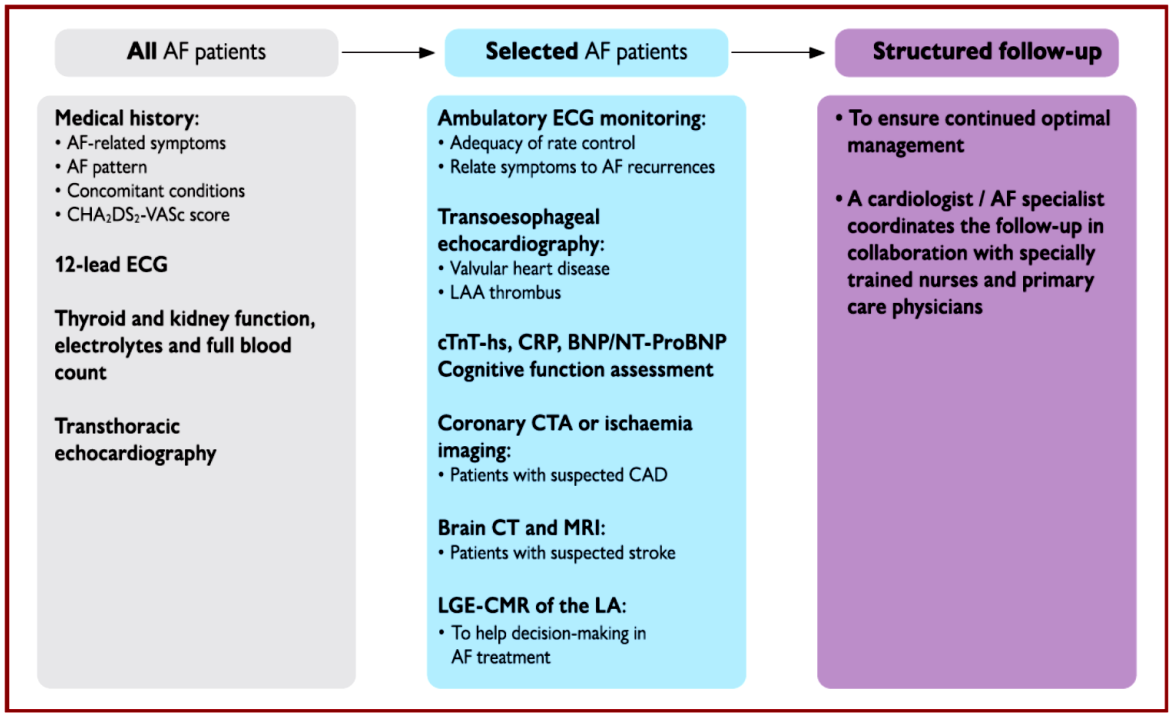


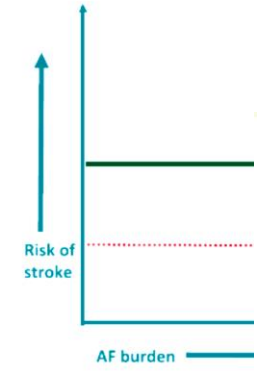
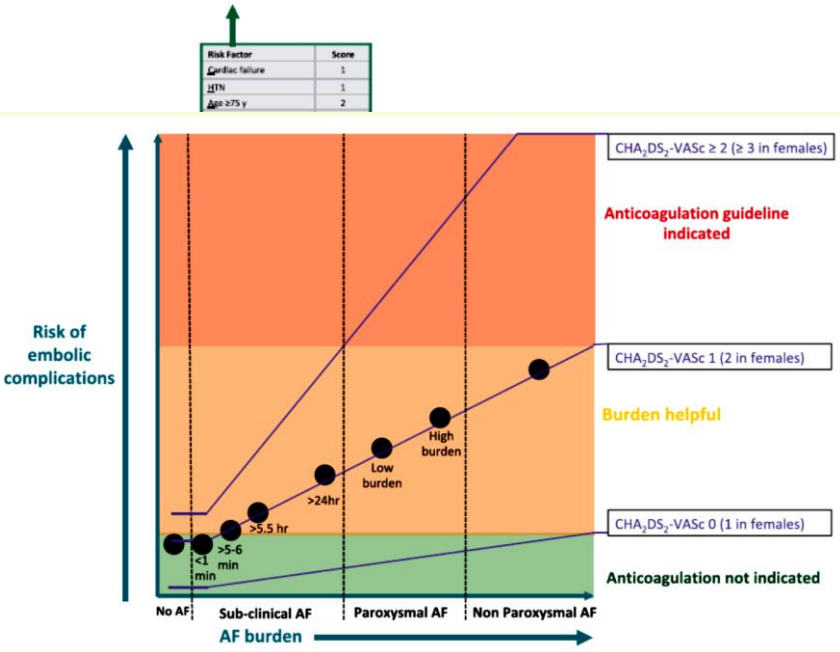
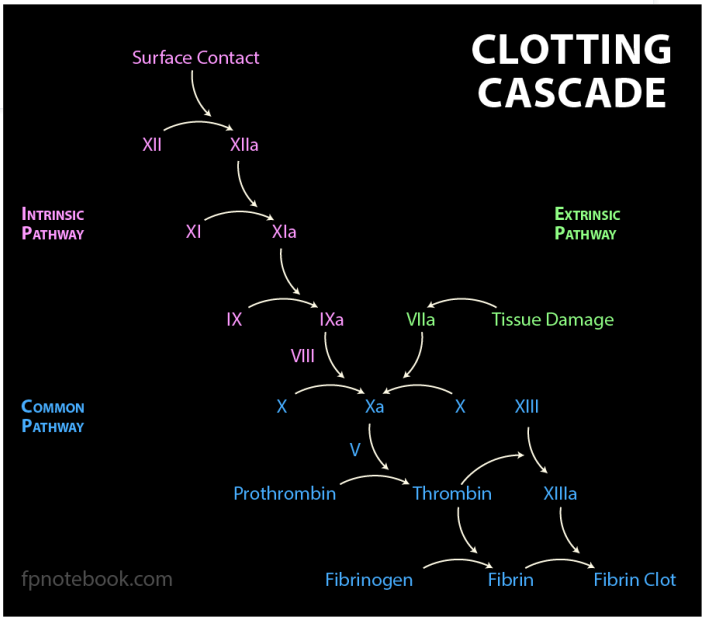


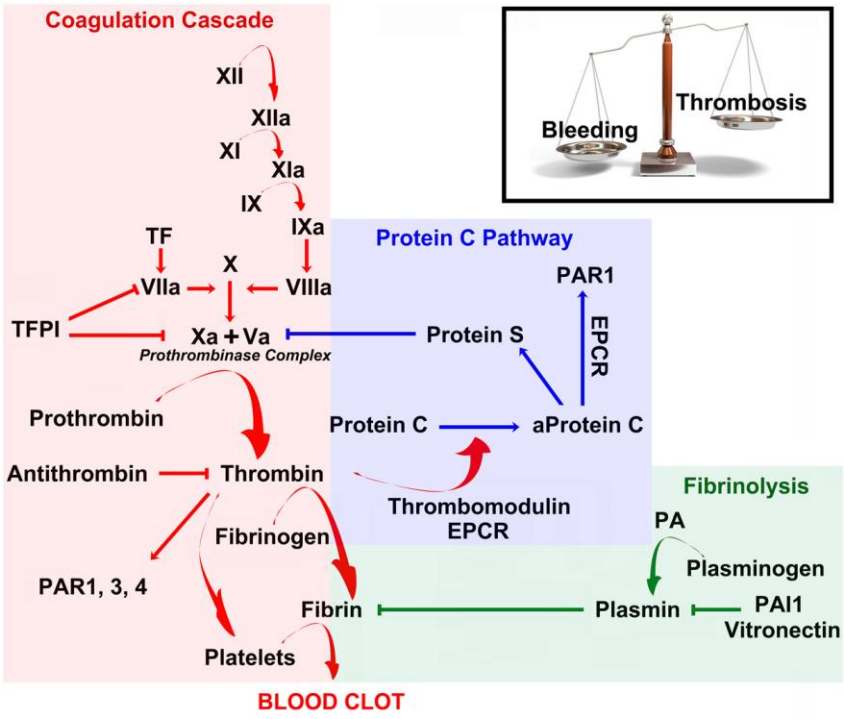
Figure 1 The traditic
reflected in the guidelines
CHA_2DS_2-VASc score al
AF, atrial fibrillation.

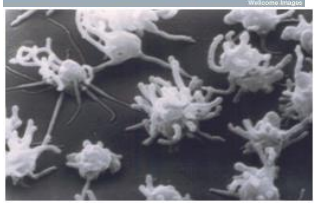


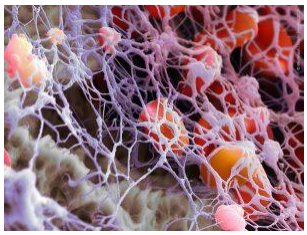
Outlines

- **Coagulation pathway**

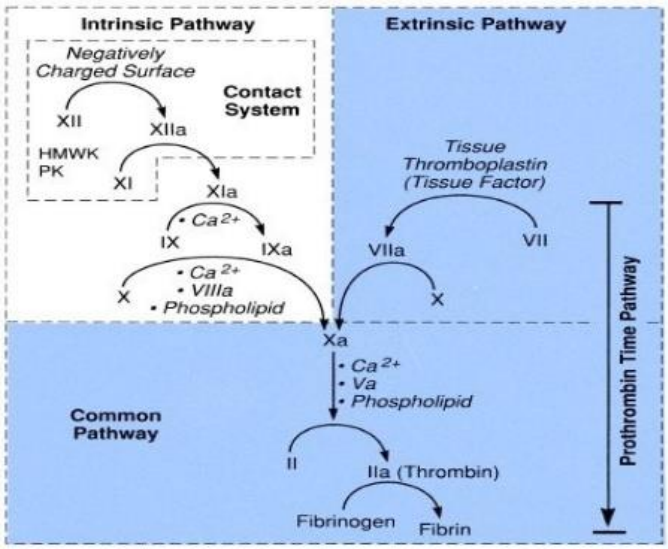








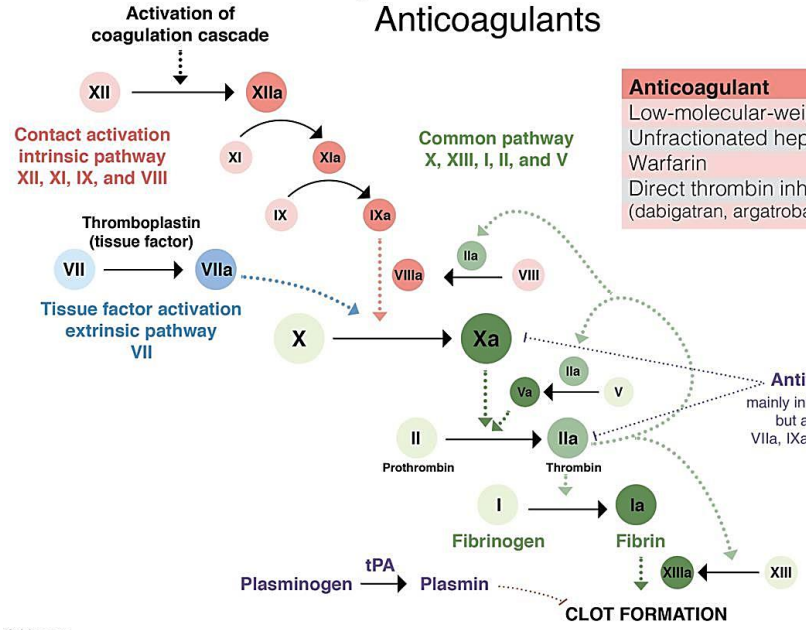
Prothombin Time



Causes of Abnormal Prothrombin Time

- Deficiencies of Factor VII
- Deficiencies of Factor X
- Deficiencies of Factor V
- Deficiencies of Factor II
- Deficiencies of Fibrinogen
- Heparin
- Warfarin
- Fibrinogen/Fibrin Degradation Products
- Lupus Anticoagulant
- Liver Disease

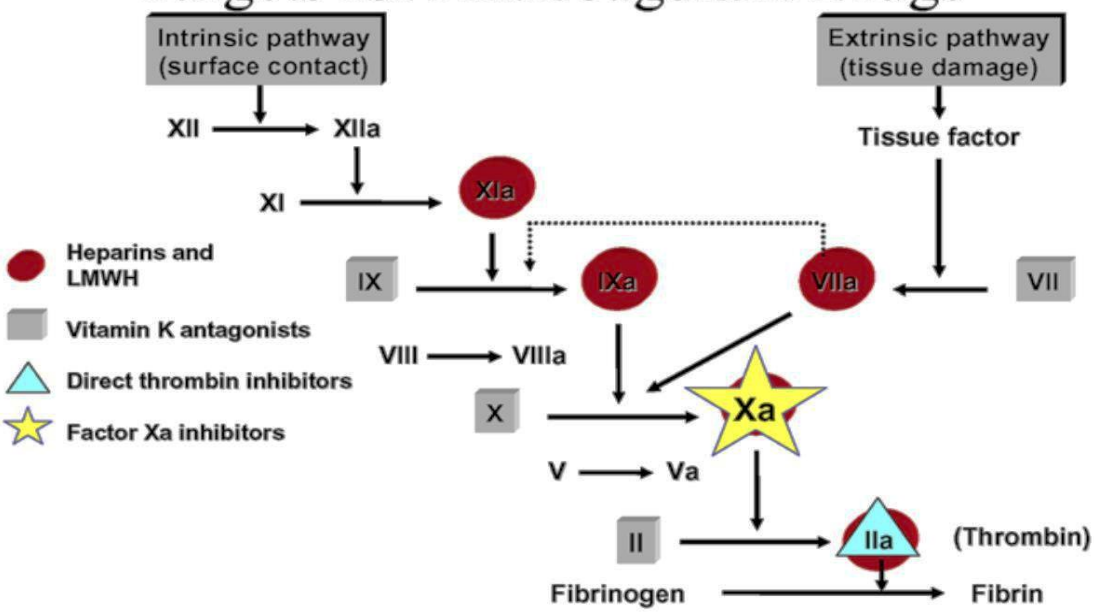
Coagulation Cascade and Anticoagulants



Anticoagulant	Factors inhibited
Low-molecular-weight heparin	Xa
Unfractionated heparin	IIa, Xa
Warfarin	IIa, VIIa, IXa, Xa
Direct thrombin inhibitor (dabigatran, argatroban, lepirudin)	IIa

Lucy Liu

Targets for Anticoagulant Drugs



Outlines

- **Comparison of NOACs**

- **Overview of oral anticoagulants**

	Mechanism	*Advantage*	*Disadvantage*
	Mechanical	**No bleeding**	**Compliance**
Coumadin	**Affects Vit K metabolism in the liver, limiting production of clotting factors II, VII, IX, X**	**Most effective**	**Difficult to reverse**
Rivaroxaban, Apixaban, Edoxaban	**Direct Xa inhibitor**	**Oral**	**Bleeding**
Dabigatran (Pradaxa)	**Direct thromBin inhibitor**		

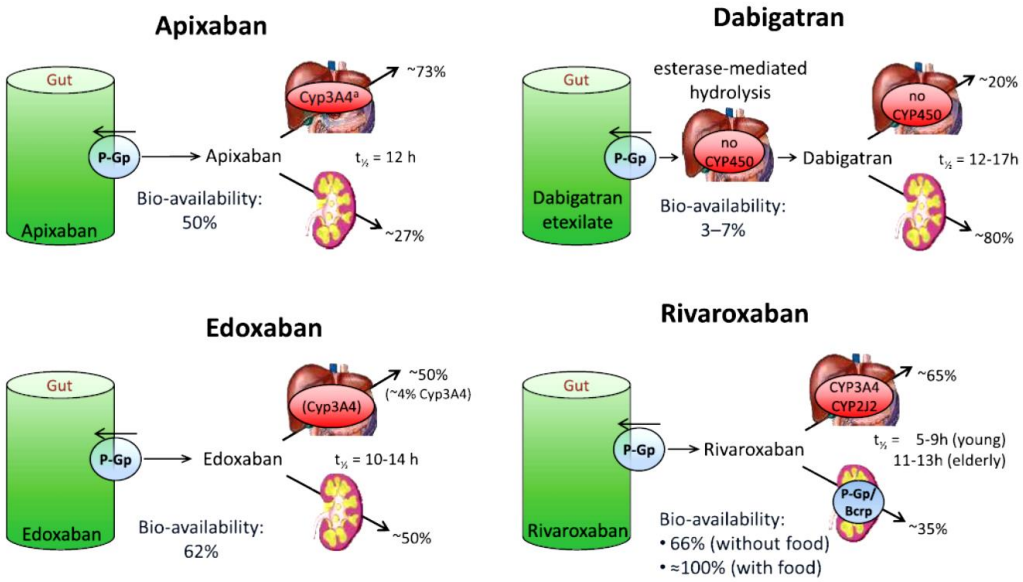


Figure 5 Absorption and metabolism of the different NOACs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. [a]Also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19. NOAC, non-vitamin K antagonist oral anticoagulant.

Table 4 Absorption and metabolism of the different NOACs

	Dabigatran[106,376]	Apixaban[517]	Edoxaban[518]	Rivaroxaban[519,520]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (In part dialysable)	14% (Not dialysable)	NA (Not dialysable)	NA (Not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%)[519], CYP2J2
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	−12% to 30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels (h)	3	3	2–4	2–4
Elimination half-life (h)	12–17	12	10–14	5–9 (young) 11–13 h (elderly)

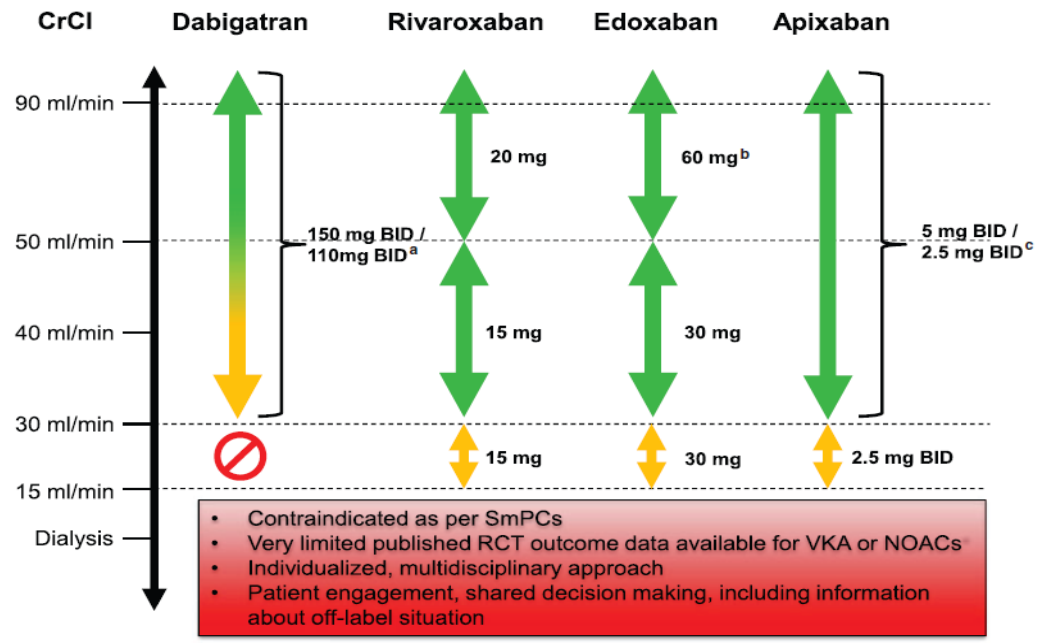
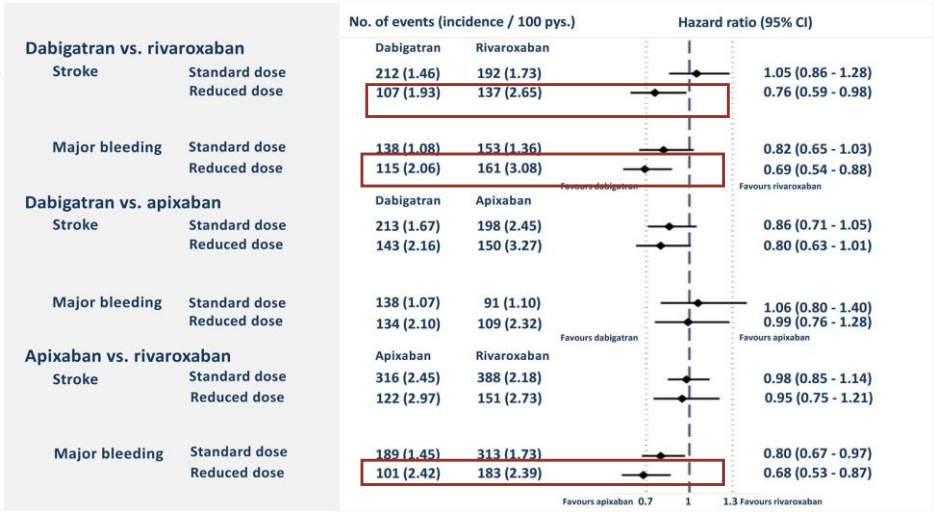


Table 11 Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: • Age ≥80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: • Age ≥80 years, • Body weight ≤60 kg, or • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of the following: • CrCl 15 - 50 mL/min, • Body weight ≤60 kg, • Concomitant use of dronedarone ciclosporine, erythromycin, or ketoconazole

b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; o.d. = *omni die* (once daily).

Figure 5 The risk of stroke or systemic embolism and major bleeding for patients using standard or reduced dose ...



Eur Heart J Cardiovasc Pharmacother, Volume 6, Issue 2, March 2020, Pages 75–85, https://doi.org/10.1093/ehjcvp/pvz086

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable
Age >65 years	Extreme frailty ± excessive risk of falls[a]	Hypertension/elevated
Previous major bleeding	Anaemia	Concomitant antiplatel
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intak
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OA
Malignancy	VKA management strategy[b]	Hazardous hobbies/oc
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with h
Previous stroke, small-vessel disease, etc.		INR control (target 2.0
Diabetes mellitus		TTR >70%[c]
Cognitive impairment/dementia		Appropriate choice of correct dosing[d]

Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137
Expected impact of NOACs on routine coagulation tests[148,150,158,549,552–554]				
PT	(↑) peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

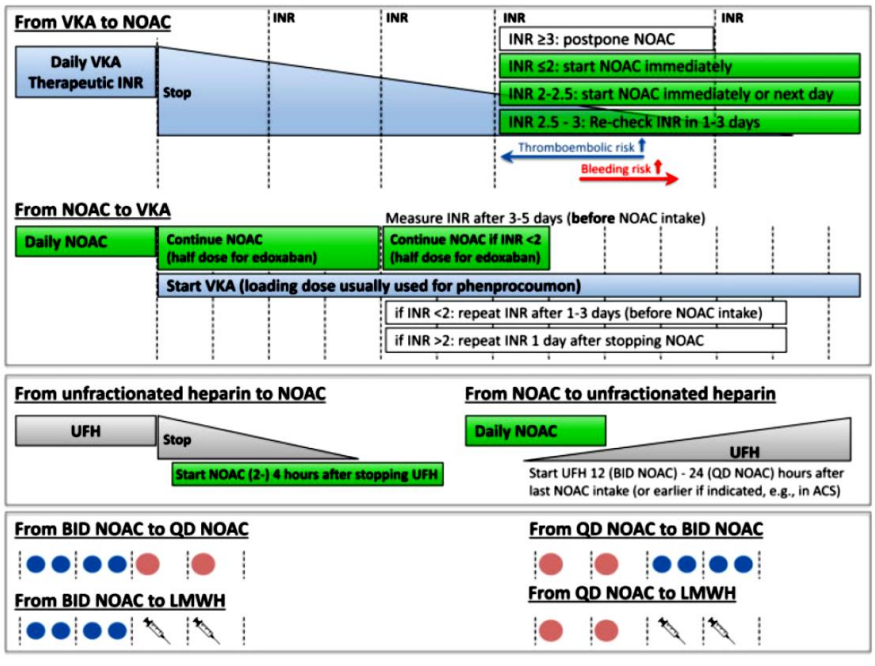
ACT, activated clotting time; AF, atrial fibrillation; aPTT, activated prothrombin time; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.
*[ng/ml] 5–95% percentiles for FXa inhibitors and 10–90% percentiles (ng/ml) for Dabigatran).

Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%[SmPC]	No PK data[a]	+40%[521-523]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[524]	No effect[523]	No effect[525]
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect[SmPC]	+40%[526]	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85%[b 523] (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%[SmPC]	No data yet	+77%[523] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180%[SmPC] (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR)[523] (no dose reduction required by label)	+40%[527] (probably not relevant)[528]

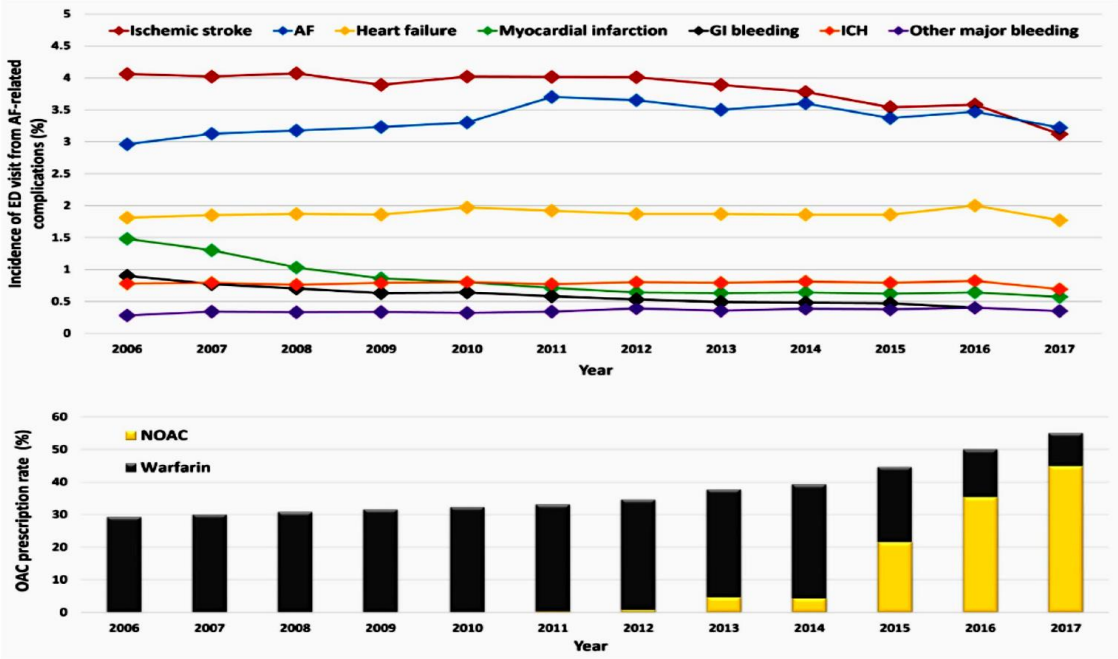
Table 5 Effect of drug-drug interactions and clinical factors on **NOAC** plasma levels and anticoagulant effects

Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction [529]	No data yet	No effect [523]	No effect [530]
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65% [SmPC] (give loading dose 2h after dabigatran) [d]	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% C_{max} (SmPC)	Clarithromycin: +60% AUC; +30% C_{max} (SmPC)	Erythromycin: +85% AUC; +68% C_{max} [531] (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% C_{max} Erythromycin: +30% AUC; +30% C_{max} (SmPC)
Rifampicin	P-gp/ BCRP and CYP3A4 induction	– 66% AUC; – 67% Cmax (SmPC)	– 54% AUC; – 42% Cmax (SmPC)	– 35% AUC, (but with compensatory increase of active metabolites) [532]	– 50% AUC; – 22% Cmax (SmPC)



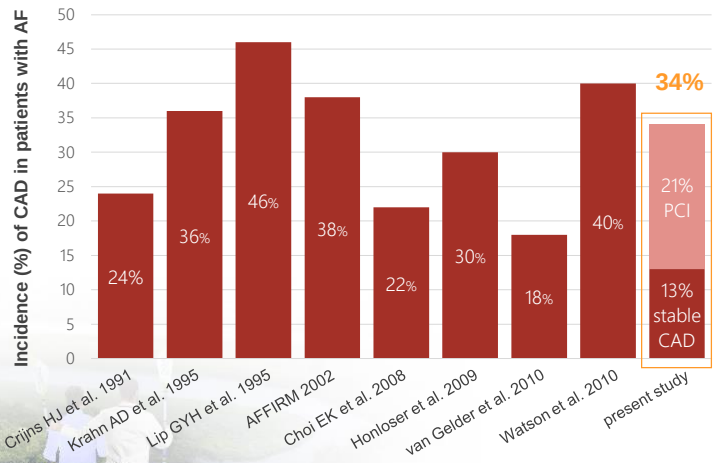
Outlines

- **Anti-coagulation in Af Pts with co-morbidity**



Chao et al. Journal of Arrhythmia. 2021;00:1–38.

Around 1/3 of AF patients have coexisting CAD*



Kralev et al. in the study of AF patients undergoing coronary angiography showed that stable CAD was diagnosed in 13% of AF patients and in 21% of the patients with CAD percutaneous coronary intervention (PCI) or CABG were performed

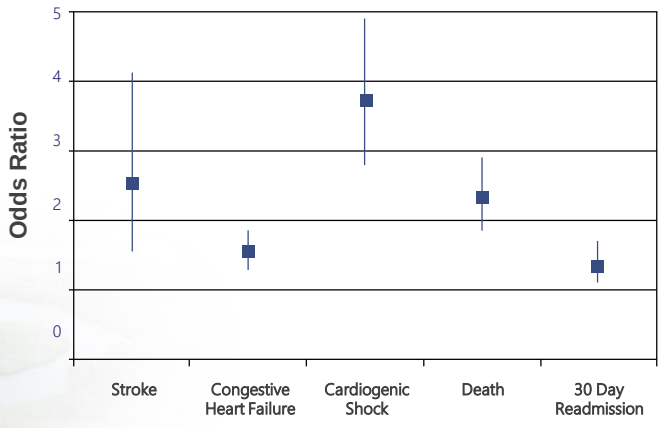
PC-TW-102732_202109

* CAD = Coronary Artery Disease
Kralev et al. PLOS ONE 6(9): e24964

Pradaxa Praxbind

Higher risks of stroke and death in patients with AF & CAD

Greater- than 2-fold higher risk for acute stroke and death during hospitalization in patients admitted with an AMI and AF

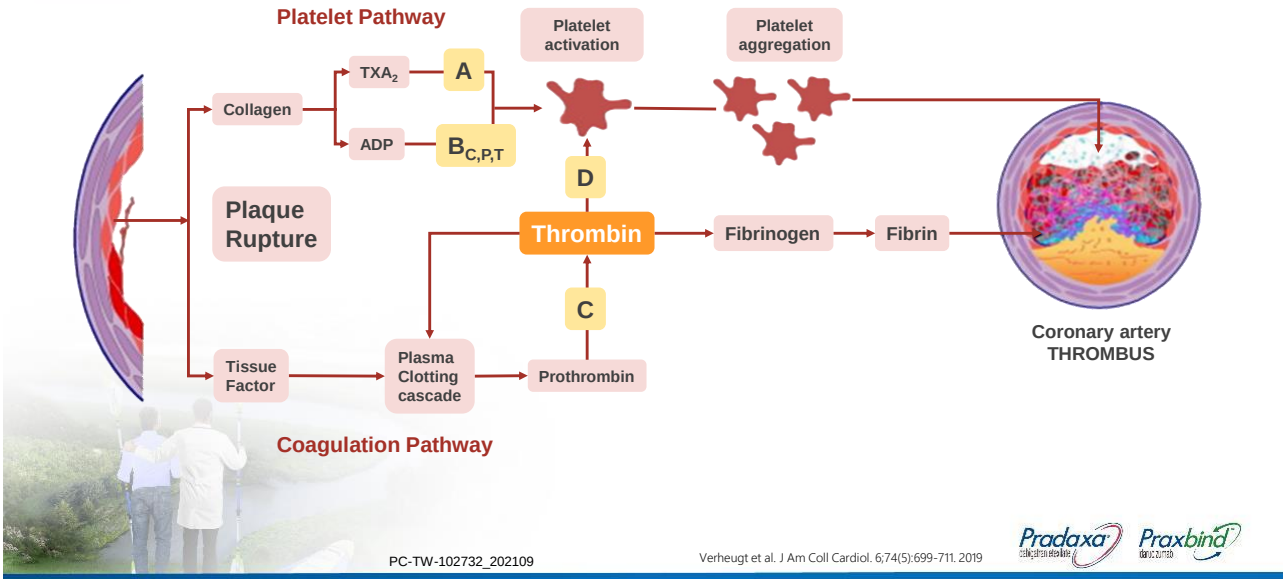


PC-TW-102732_202109

Kundu et al. Am J Cardiol. 2016; 117(8): 1213–1218.

Pradaxa Praxbind

Antithrombotic therapy as secondary prevention for patients either with stable ischemic heart disease or after acute coronary syndromes (ACS)

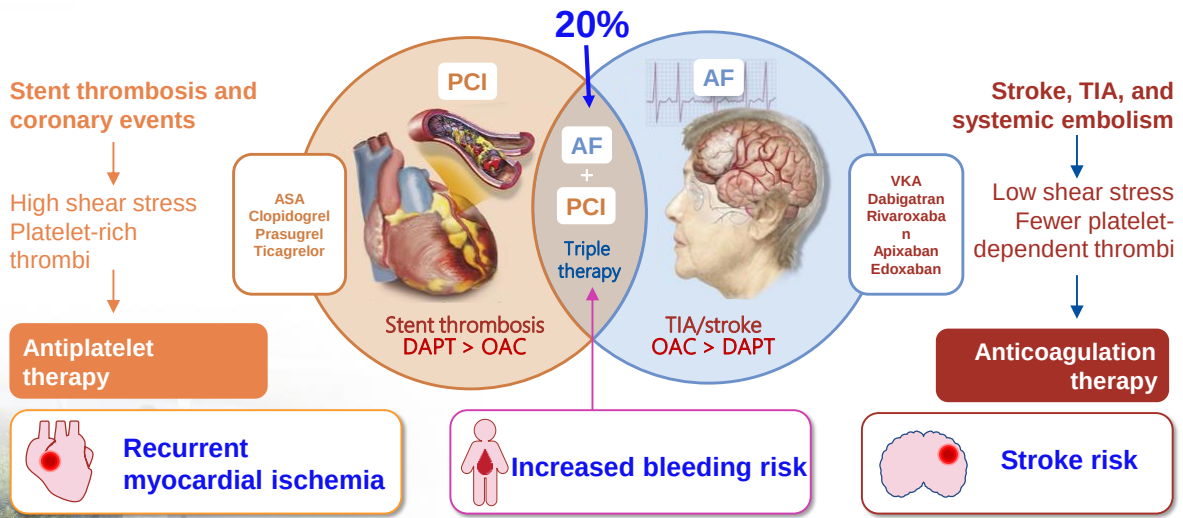


PC-TW-102732_202109

Verheugt et al. J Am Coll Cardiol. 6;74(5):699-711. 2019

Pradaxa Praxbind

Management of patients with AF must balance the risk of bleeding with the risk of thrombosis



ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; TIA, transient ischemic attack

Capodanno, Angiolillo. JACC Cardiovasc Interv 2017;10:1086; Effron, Gibson. Prog Cardiovasc Dis 2018;60:531

PC-TW-102732_202109

Pradaxa Praxbind

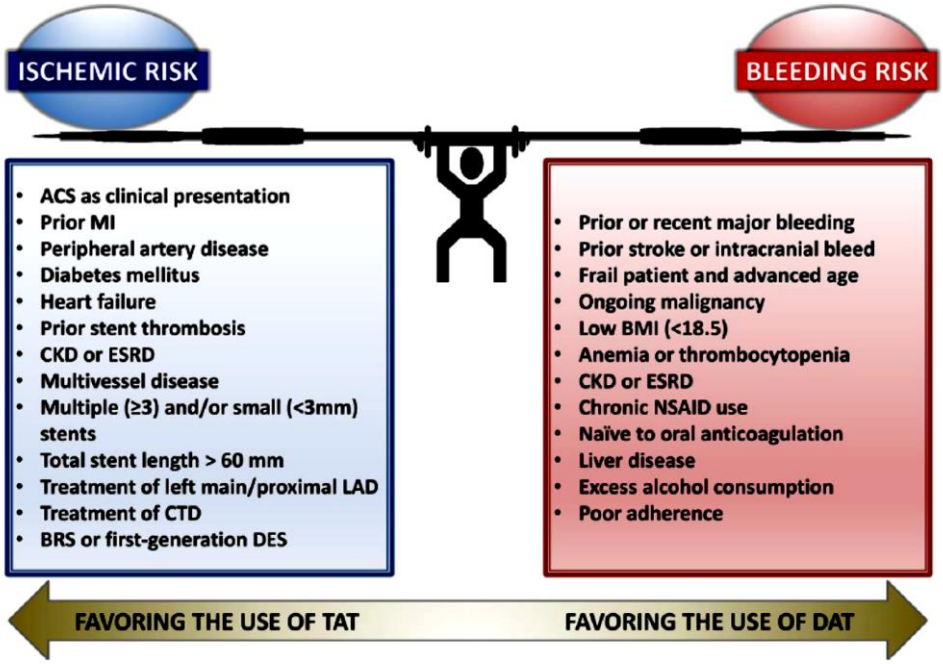
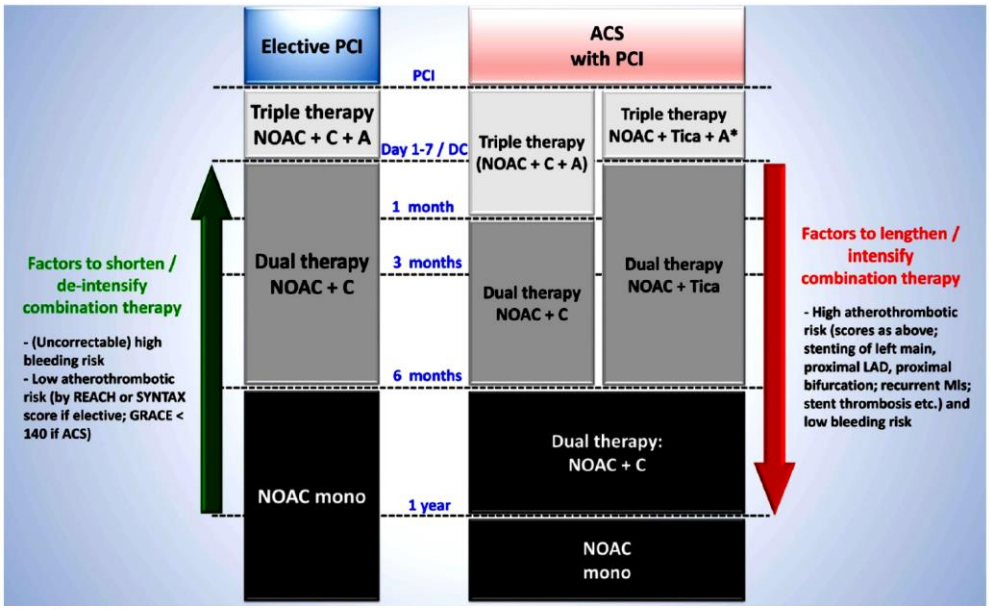


TABLE 2 Summary of four randomized clinical trials in patients with coronary artery disease and atrial fibrillation[118–121]

	PIONEER-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF PCI
No. of participating patients (Asian patients, %)	2124 (4.0%)	2725 (NA)	4614 (3.1%)	1506 (11.2%)
Randomization	• Rivaroxaban 15 mg + a P2Y12 inhibitor (group 1) • Rivaroxaban 2.5 mg + DAPT (group 2) • VKA + DAPT (group 3)	• Dabigatran 110 mg + a P2Y12 inhibitor • Dabigatran 150 mg + a P2Y12 inhibitor • VKA + DAPT • (except US, dabigatran 110 mg + a P2Y12 inhibitor or VKA + DAPT for elderly patients)	A 2X2 factorial design • Apixaban 5 mg versus VKA • Aspirin versus placebo	• Edoxaban 60 mg + a P2Y12 inhibitor versus VKA + DAPT
Duration from the PCI to randomization	Within 72 h	Within 120 h	Within 14 days	4 h to 5 days
Primary endpoint	Major or minor bleeding	Major or minor bleeding	Major or minor bleeding	Major or minor bleeding
Hazard ratio for the primary endpoint	Group 1 versus group 3: 0.59 (0.47–0.76) group 2 versus group 3: 0.63 (0.50–0.80)	Dabigatran 110 mg versus VKA + DAPT: 0.52 (0.42–0.63) Dabigatran 150 mg versus VKA + DAPT: 0.72 (0.58–0.88)	Apixaban 5 mg versus VKA: 0.69 (0.58–0.81) Aspirin versus placebo: 1.89 (1.59–2.24)	edoxaban + a P2Y12 inhibitor versus VKA + DAPT: 0.83 (0.65–1.05)

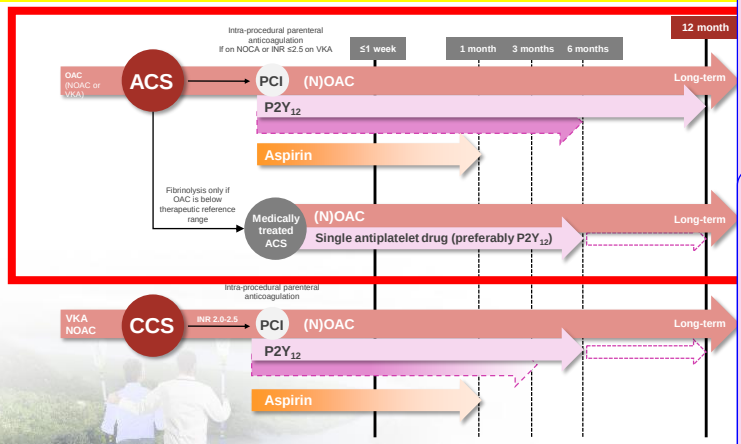


In all patients:
- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

*If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data)

2020 ESC Recommendations for patients with AF and an ACS, PCI, or CCS

- Dual antithrombotic therapy including OAC and a P2Y12 inhibitor is associat
  ICH) than triple therapy.
- At least a short course of triple therapy (e.g. <_1 week) would be desirable in
  undergoing PCI, especially in those at increased risk of ischaemic events.



THROMBOTIC RISK FACTORS
- Diabetes melitus requiring therapy
- Prior ACS/recurrent myocardial infarction
- Multivessel CAD
- Concomitant PAD
- Premature CAD (occurring at age of <45y) or accelerated CAD (new lesion within 2 years)
- CKD (eGFR <60 mL/min)

BLEEDING RISK FACTORS
- Hypertension
- Abnormal renal or liver function
- Stroke or ICH history
- Bleeding history or bleeding diathesis (e.g., anaemia with haemoglobin <110 g/L)
- Labile INR (if on VKA)
- Elderly (<65 years)
- Drugs (concomitant OAC and antiplatelet therapy, NSAIDs), excessive alcohol consumption

PC-TW-102732_202109

Hindricks et al., European Heart Journal (2020)42,373-498

Secondary prevention of atherothrombotic events post-ACS in patients without AF (i.e. no OAC indication)

	Standard dose	Comments/dose reduction
Rivaroxaban[115]	2.5 mg BID	In addition to aspirin ± P2Y12 inhibitor

BID, twice daily.

Secondary prevention of atherothrombotic events in patients with chronic coronary syndrome and/or symptomatic peripheral artery disease patients without AF (i.e. no OAC indication)

	Standard dose	Comments/dose reduction
Rivaroxaban[516]	2.5 mg BID	In addition to aspirin

AF, atrial fibrillation; BID, twice daily; OAC, oral anticoagulation.

Treatment for VTE and PE

Table 2 OACs and approved/studied doses across indications

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban[47]	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran[48]	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban[49]	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban[46]	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban[498]	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran[499]	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban[500]	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban[501,502]	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.
[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].
[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban[503]	2.5 mg BID	
Dabigatran[504]	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban[473,500,505]	60 mg QD[b]	
Rivaroxaban[506]	10 mg QD	[c]

BID, twice daily; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).
[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.
[c]SmPc: 20 mg QD in patients at high risk of recurrence.

VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban[507]	2.5 mg BID	
Dabigatran[508,509]	220 mg QD/150 mg QD	[a]
Edoxaban[510,511]	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban[512–515]	10 mg QD	

BID, twice daily; QD, once daily.
[a]SmPc: 1 × 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.

NOACs in patients with liver disease

Baseline assessment:
- H/o thromboembolism or bleeding?
- Relevant co-medications and over-the-counter drugs?
- CBC, liver function test, PT/INR, aPTT, renal function
- High bleeding risk (e.g., H/o major bleeding (varices), uncontrolled alcohol intake, etc.)?

Highest risk patients → **Consider no anticoagulation / evaluate alternative stroke prevention strategy**

All other patients

Parameter	1 point	2 points	3 points
Encephalo-pathy	No	Grade 1-2	Grade 3-4
Ascites	No	Mild	≥ Moderate
Bilirubin	< 2 mg/dL < 34 µmol/L	2-3 mg/dL 34-50 µmol/L	> 3 mg/dL > 50 µmol/L
Albumin	> 3.5 g/dL > 35 g/L	2.8-3.5 g/dL 28-35 g/L	< 2.8 g/dL < 28 g/dL
INR	< 1.7	1.71-2.30	>2.30

NOAC Use recommendations in liver disease

	A (<7 pts)	B (7-9 pts)	C (>9 pts)
Dabigatran	Normal dose	Use with caution	Not recommended
Apixaban			
Edoxaban			
Rivaroxaban		Not recommended	

- ✓ Assess Child-Pugh score
- ✓ Check NOAC use recommendations in liver disease
- ✓ Check for drug-drug interactions
- ✓ Discuss in multidisciplinary team

Close follow-up (see also Fig. 3)
- Signs of (occult) bleeding?
- Adherence? Side effects?
- (New) co-medications, incl. NSAIDs, aspirin, OTC?
- CBC, liver function, PT/INR, aPTT, renal function
- Continue bleeding risk minimization strategies
- Re-enforce education, incl. alcohol abstinence

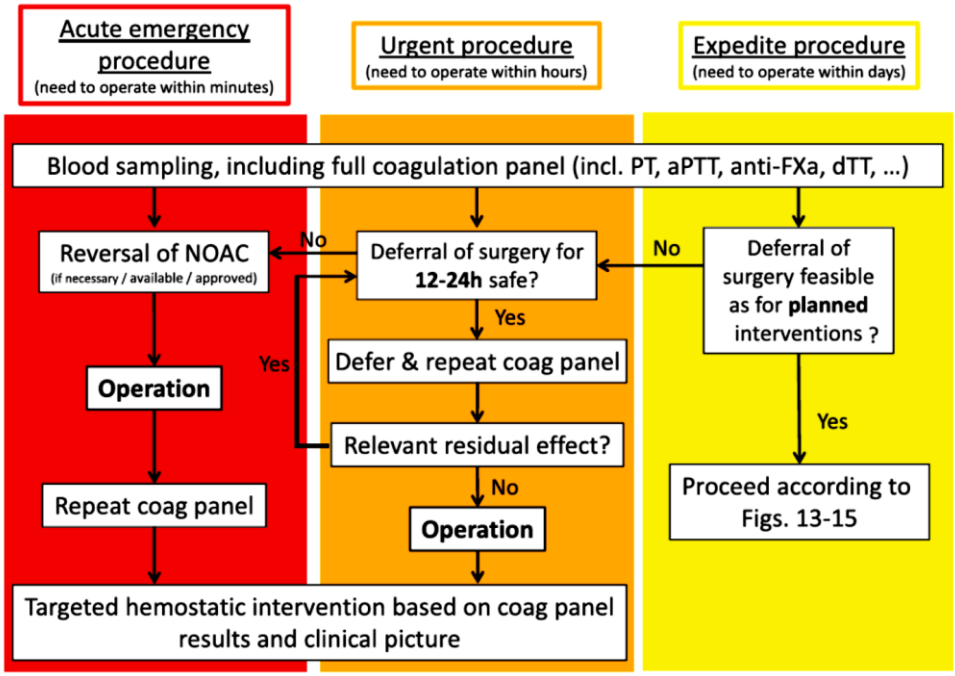


Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137
Expected impact of NOACs on routine coagulation tests[148,150,158,549,552–554]				
PT	(↑) peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

ACT, activated clotting time; AF, atrial fibrillation; aPTT, activated prothrombin time; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.
*[ng/ml] 5–95% percentiles for FXa inhibitors and 10–90% percentiles (ng/ml) for Dabigatran).

Table 12 Classification of elective surgical interventions according to bleeding risk

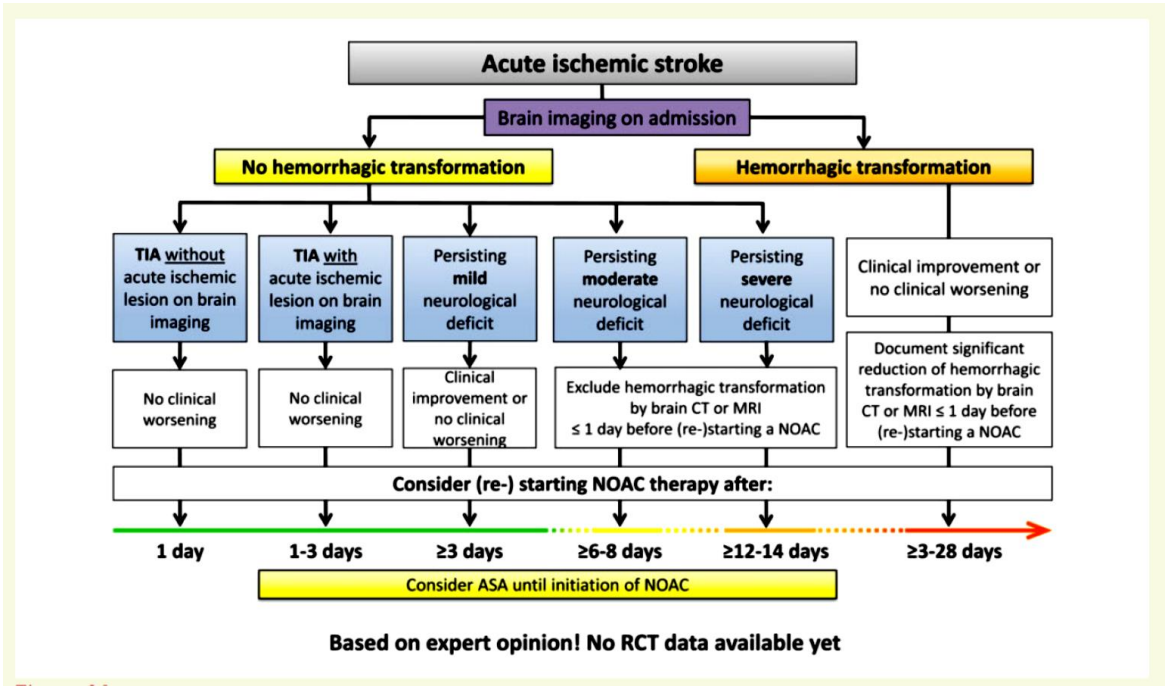
Minor risk interventions (i.e. infrequent bleeding and with low clinical impact)
Dental extractions (1–3 teeth), paradontal surgery, implant positioning, subgingival scalling/cleaning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions, skin biopsy)
Pacemaker or ICD implantation (except complex procedures)
Electrophysiological study or catheter ablation (except complex procedures)
Routine elective coronary/peripheral artery intervention (except complex procedures)
Intramuscular injection (e.g. vaccination)
Low-risk interventions (i.e. infrequent bleeding or with non-severe clinical impact)
Complex dental procedures
Endoscopy with simple biopsy
Small orthopaedic surgery (foot, hand, arthroscopy, . . .)
High-risk interventions (i.e. frequent bleeding and/or with important clinical impact)
Cardiac surgery
Peripheral arterial revascularization surgery (e.g. aortic aneurysm repair, vascular bypass)
Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.
Neurosurgery
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Complex endoscopy (e.g. multiple/large polypectomy, ERCP with sphincterotomy etc.)
Abdominal surgery (incl. liver biopsy)
Thoracic surgery
Major urologic surgery/biopsy (incl. kidney)
Extracorporeal shockwave lithotripsy
Major orthopaedic surgery

Table 1 Selected indications and contraindications for NOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome[15,16]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease[12,17–22] Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA[24] Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT[25,26]
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs[33–36]

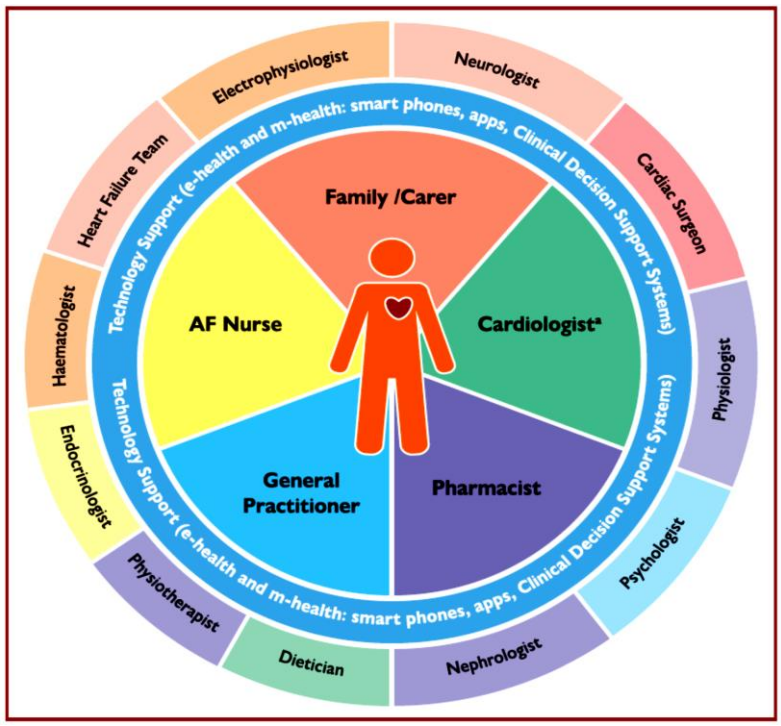
Table 12 Antithrombotic therapy after left atrial appendage occlusion

Device/patient	Aspirin	OAC	Clopidogrel	Comments
Watchman/low bleeding risk	75-325 mg/day indefinitely	Start warfarin after procedure (target INR 2-3) until 45 days or continue until adequate LAA sealing is confirmed[a] by TOE. NOAC is a possible alternative	Start 75 mg/day when OAC stopped, continue until 6 months after the procedure	Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)
Watchman/high bleeding risk	75-325 mg/day indefinitely	None	75 mg/day for 1-6 months while ensuring adequate LAA sealing[a]	Clopidogrel often given for shorter time in very high-risk situations
ACP/Amulet	75-325 mg/day indefinitely	None	75 mg/day for 1-6 months while ensuring adequate LAA sealing[a]	Clopidogrel may replace long-term aspirin if better tolerated



Outlines

- **Summary**



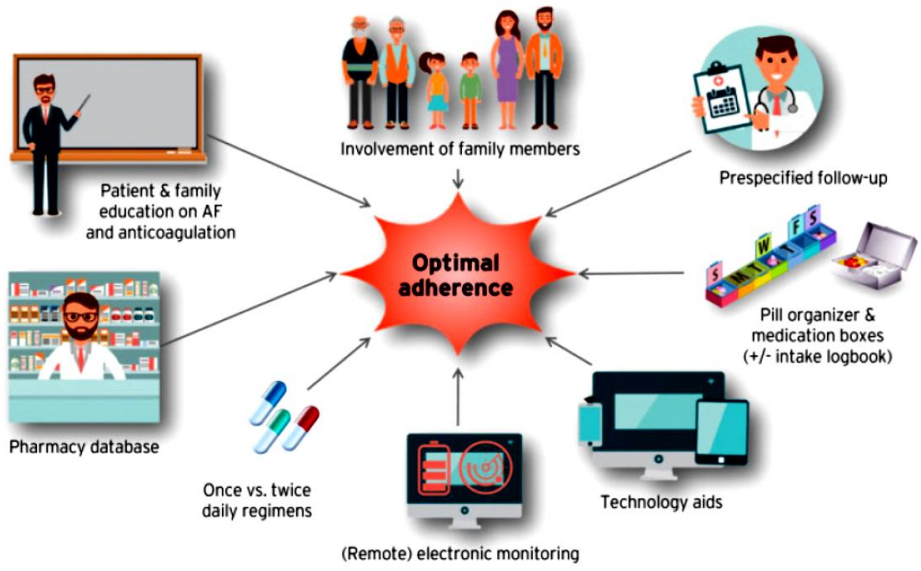


Figure 1 Selection of possibilities to increase adherence to NOACs. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

The ABC pathway for integrated care management

'A' Avoid stroke
Optimize stroke prevention

'B' Better symptom management
Treat symptoms

'C' Cardiovascular and other comorbidities
Manage risk factors

'Atrial fibrillation 3-step'

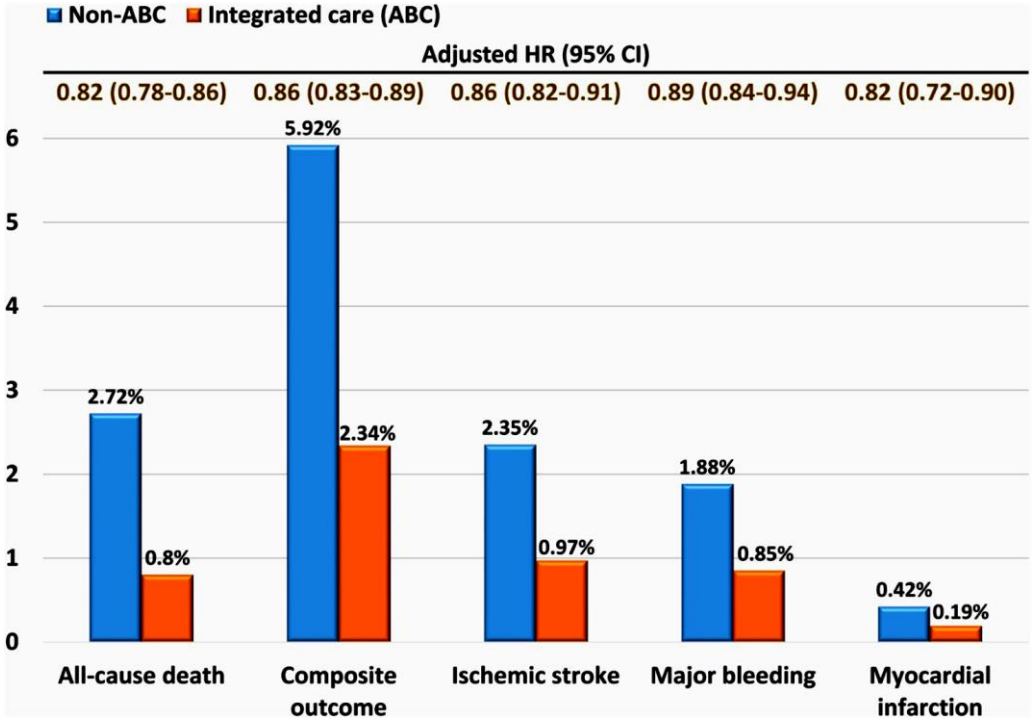
Patient-centered and symptom-directed decisions on rate or rhythm control

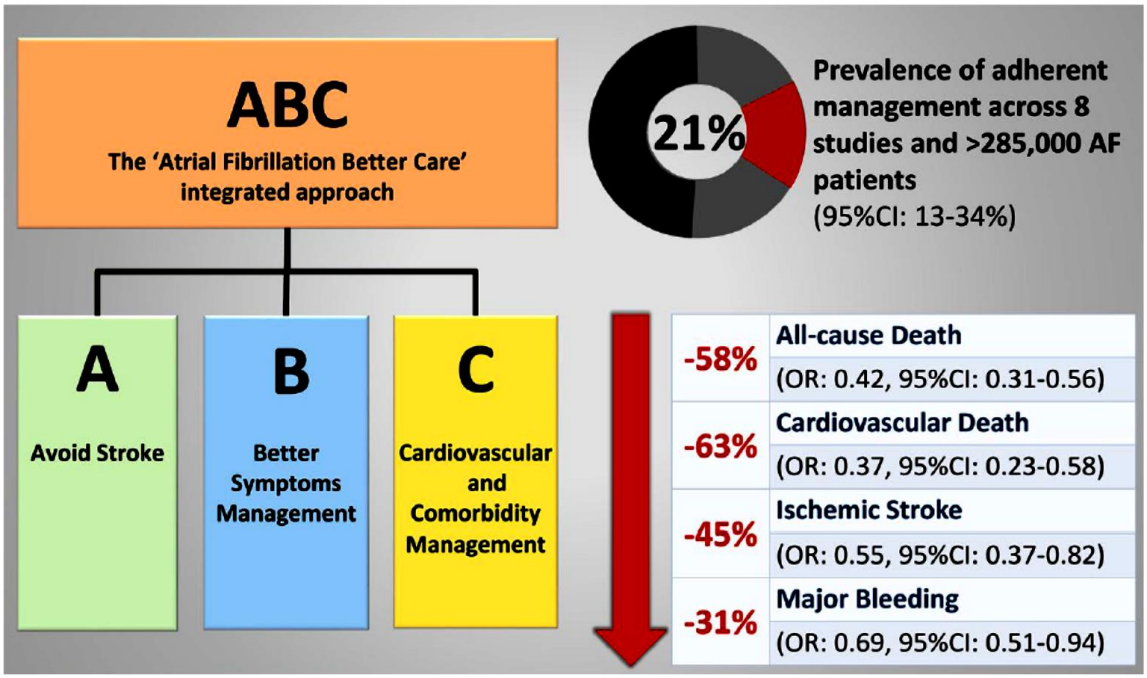
- **Manage hypertension, heart failure, diabetes mellitus, cardiac ischemia, and sleep apnea**
- **Lifestyle changes: obesity reduction, regular exercise, and reduction of alcohol and stimulant use**
- **Patient psychological morbidity**
- **Consider patient values and preferences**

Step 1
- **Identify low risk patients**

Step 2
- **Offer stroke prevention to patients with one or more risk factors for stroke**
- **Assess bleeding risk**

Step 3
- **Decide on OACs (either a NOAC [preferred] or VKA with well-managed TTR)**


Non-ABC
Integrated care (ABC)
Adjusted HR (95% CI)
0.82 (0.78-0.86)
0.86 (0.83-0.89)
0.86 (0.82-0.91)
0.89 (0.84-0.94)
0.82 (0.72-0.90)
6
5
4
3
2
1
0
2.72%
0.8%
5.92%
2.34%
2.35%
0.97%
1.88%
0.85%
0.42%
0.19%
All-cause death
Composite outcome
Ischemic stroke
Major bleeding
Myocardial infarction


ABC
The 'Atrial Fibrillation Better Care' integrated approach
A
Avoid Stroke
B
Better Symptoms Management
C
Cardiovascular and Comorbidity Management
21%
Prevalence of adherent management across 8 studies and >285,000 AF patients
(95%CI: 13-34%)
-58%
All-cause Death
(OR: 0.42, 95%CI: 0.31-0.56)
-63%
Cardiovascular Death
(OR: 0.37, 95%CI: 0.23-0.58)
-45%
Ischemic Stroke
(OR: 0.55, 95%CI: 0.37-0.82)
-31%
Major Bleeding
(OR: 0.69, 95%CI: 0.51-0.94)

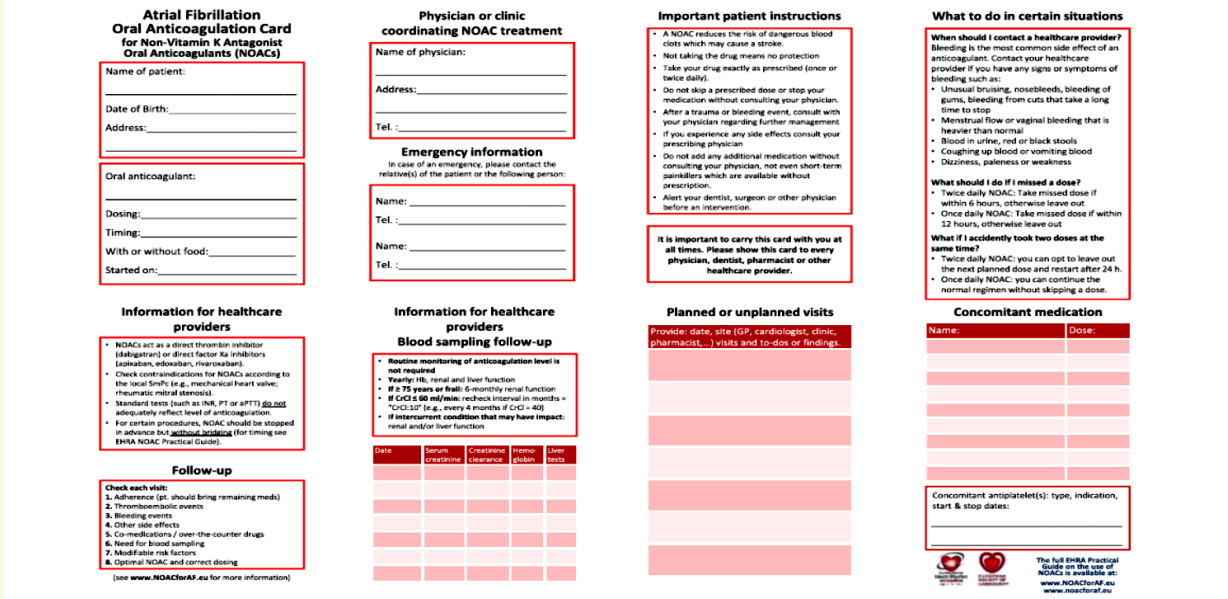


Figure 2 The EHRA NOAC card. A patient information card is crucial, both for the patient (instructions on correct intake; contact information in case of questions) as for healthcare providers. This generic and universal card should document each visit, each relevant observation or examination, and any medication change. EHRA, European Heart Rhythm Association; NOAC, non-vitamin K antagonist oral anticoagulant.

Important patient instructions | **What to do in certain situations**

Missed dose

A forgotten dose may be taken until half of the dosing interval has passed. Hence, <u>for NOACs with a twice daily (BID) dosing regimen (i.e., intake every 12 h), a forgotten full dose can be taken up until 6 h</u> after the scheduled intake. <u>For NOACs with a once daily (QD) dosing regimen, a forgotten dose can be taken up until 12 h after the scheduled intake.</u> After these time points, the dose should be skipped, and the next scheduled dose should be taken.

all times. Please show this card to every physician, dentist, pharmacist or other healthcare provider.

same time?
- Twice daily NOAC: you can opt to leave out the next planned dose and restart after 24 h.
- Once daily NOAC: you can continue the normal regimen without skipping a dose.

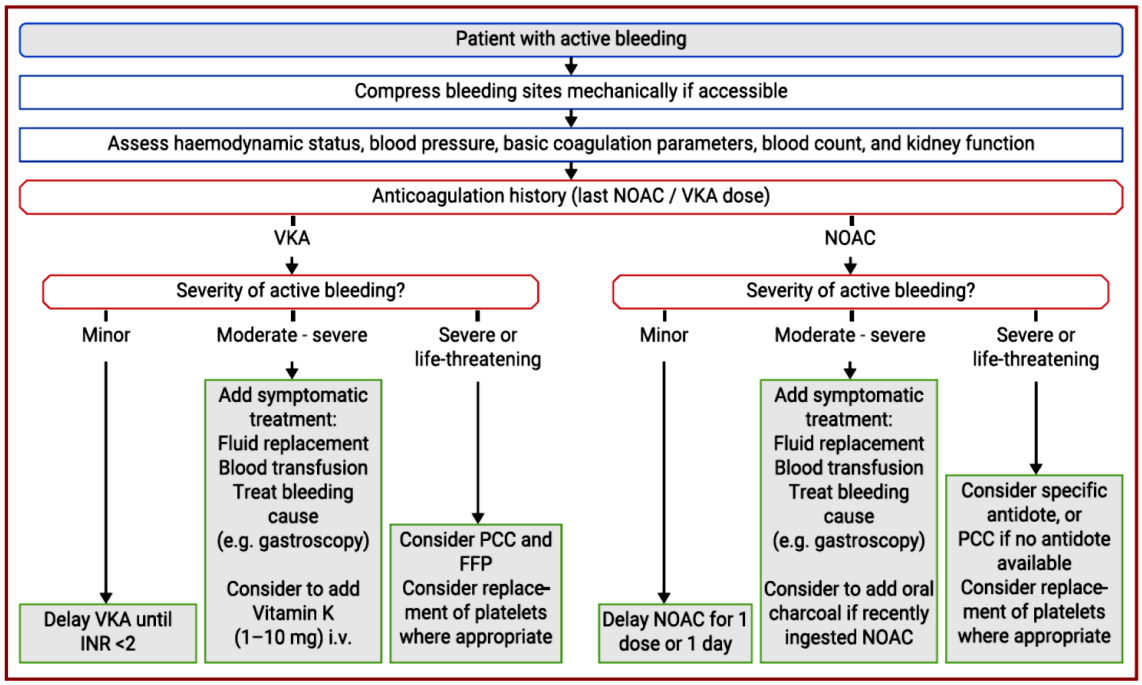
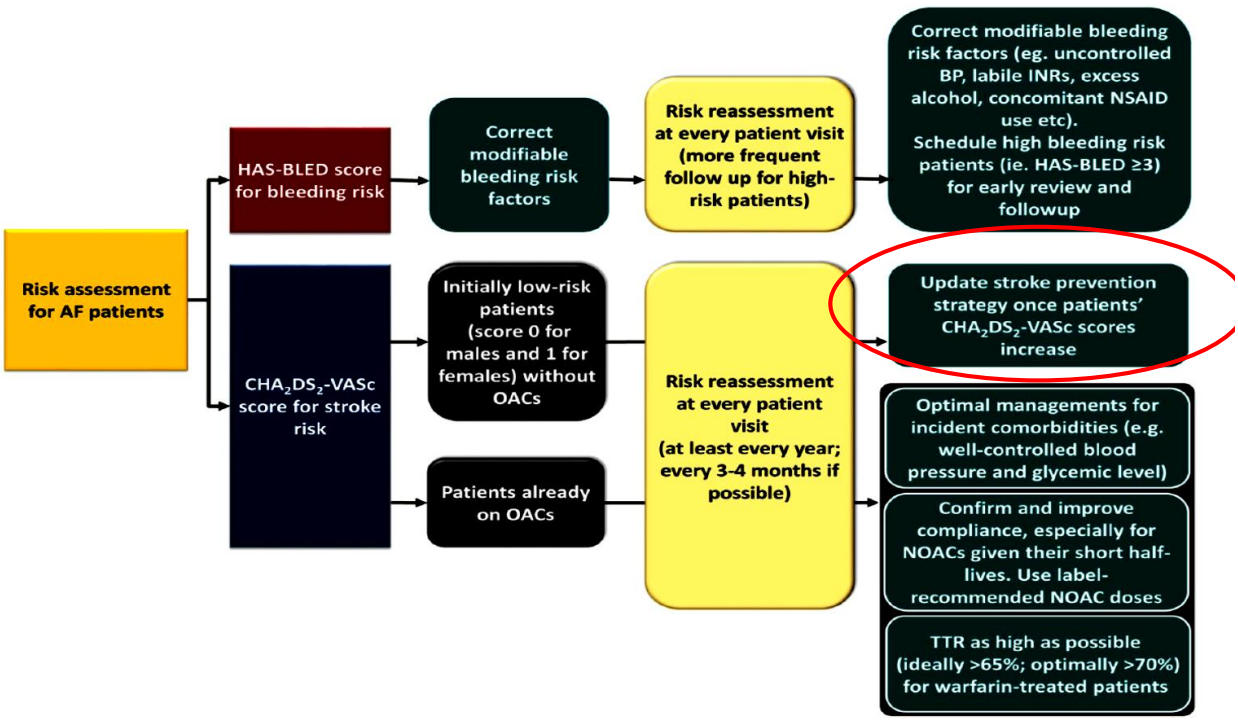


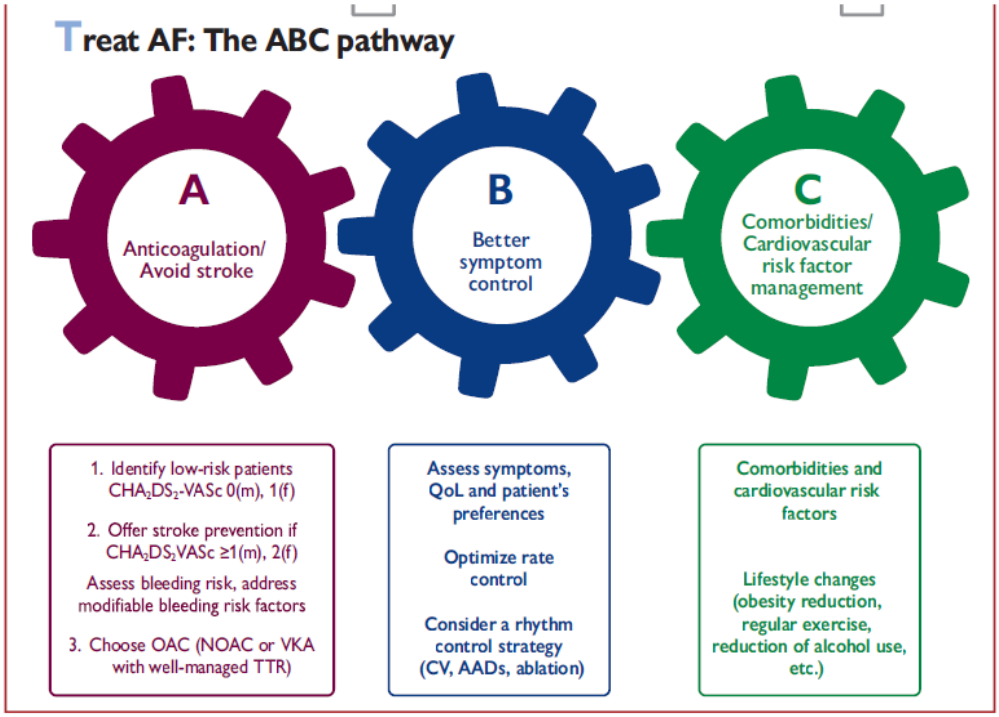
Table 10 Clinical risk factors in the HAS-BLED score[395]

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 μmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR**[b] TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

Outlines

- **Take home message**




Treat AF: The ABC pathway
A
Anticoagulation/ Avoid stroke
B
Better symptom control
C
Comorbidities/ Cardiovascular risk factor management
1. Identify low-risk patients CHA_2DS_2-VASc 0(m), 1(f)
2. Offer stroke prevention if CHA_2DS_2VASc ≥1(m), 2(f)
Assess bleeding risk, address modifiable bleeding risk factors
3. Choose OAC (NOAC or VKA with well-managed TTR)
Assess symptoms, QoL and patient's preferences
Optimize rate control
Consider a rhythm control strategy (CV, AADs, ablation)
Comorbidities and cardiovascular risk factors
Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.)
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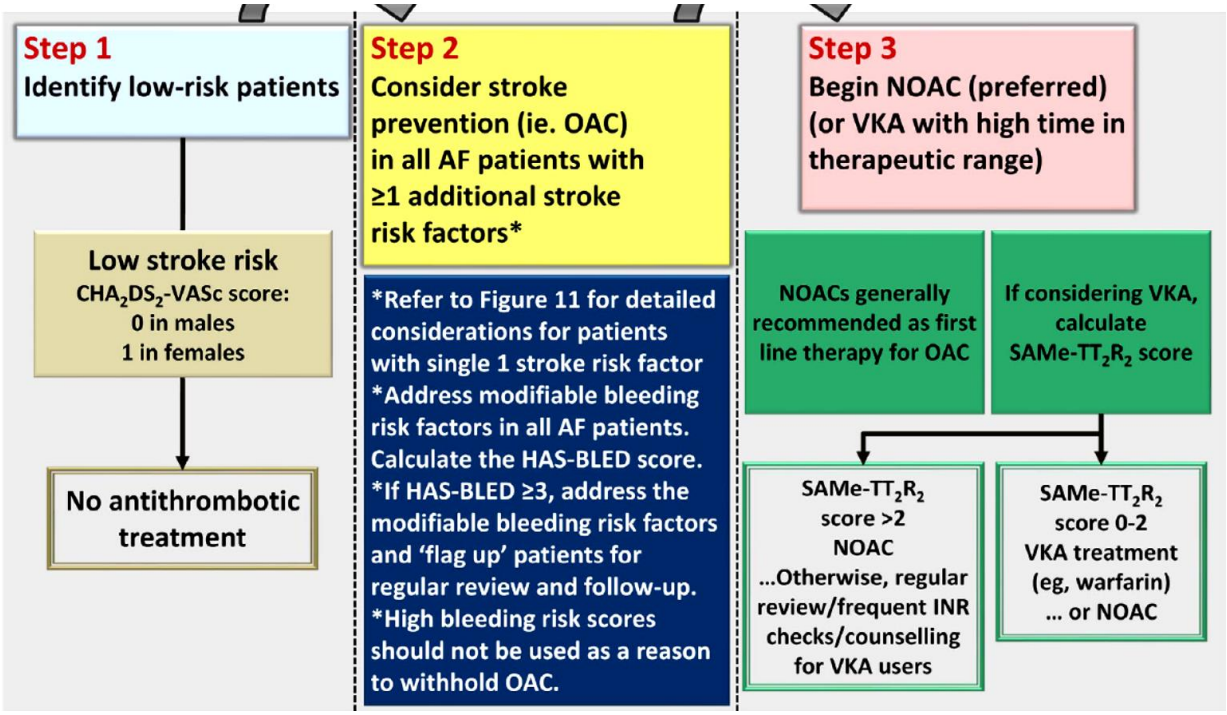
Step 1
Identify low-risk patients
Low stroke risk
CHA_2DS_2-VASc score:
0 in males
1 in females
No antithrombotic treatment
Step 2
Consider stroke prevention (ie. OAC) in all AF patients with ≥1 additional stroke risk factors*
*Refer to Figure 11 for detailed considerations for patients with single 1 stroke risk factor
*Address modifiable bleeding risk factors in all AF patients. Calculate the HAS-BLED score.
*If HAS-BLED ≥3, address the modifiable bleeding risk factors and 'flag up' patients for regular review and follow-up.
*High bleeding risk scores should not be used as a reason to withhold OAC.
Step 3
Begin NOAC (preferred) (or VKA with high time in therapeutic range)
NOACs generally recommended as first line therapy for OAC
If considering VKA, calculate SAMe-TT_2R_2 score
SAMe-TT_2R_2 score >2
NOAC
...Otherwise, regular review/frequent INR checks/counselling for VKA users
SAMe-TT_2R_2 score 0-2
VKA treatment (eg, warfarin)
... or NOAC

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Thank You for Your Attention