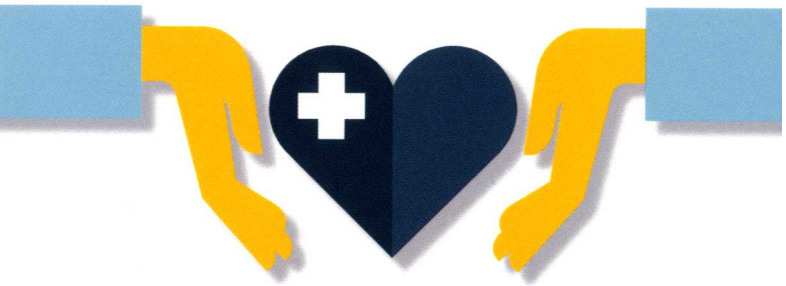
Atrial Fibrillation

A Step By Step Guide



Diagnosing Atrial Fibrillation and Non-Valvular Atrial Fibrillation Related Stroke Risk Assessment and Management

A STEP BY STEP GUIDE

1. Confirm AF with a good quality 12 lead ECG. V1 &2 are the best leads to spot 'p' waves
2. If unstable or breathless on mild exertion or rest consider admitting
3. Score AF Stroke Risk using CHA2DS2-VASc
4. Score Bleeding Risk using HAS-BLED

A STEP BY STEP GUIDE

5 Use HAS-BLED score to manage bleeding risk factors, rather than to exclude people from anticoagulation

6 Offer anticoagulation depending on score at time of diagnosis, 'Don't wait to anticoagulate'

7 Offer choice of warfarin or NOAC

8 Ensure good INR control

9 Ensure NOAC compliance and renal clearance are adequate

10 Review all NOAC patients 6 monthly

TOP TIP:
Divide creatinine clearance by 10 = monthly frequency of monitoring of U+Es

Assessing Non-Valvular Atrial Fibrillation Related Stroke Risk

CHA2DS2-VASc	SCORE
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD aortic plaque)	1
Aged 65 to 74 years	1
Sex category (i.e. female sex)	1
MAXIMUM SCORE	**9**

Outcome of Scores

CHA2DS2-VASc Clinical Risk Estimation
Adapted from Lip et al

PERCENTAGES REFER TO ANNUAL STROKE RISK

0	0.84%
1	1.75% (Previous estimate 1.3%)
2	2.69% (Previously 2.2%)
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7% (small numbers)
9	15.2%

Assessing Bleeding Risk

HAS-BLED is the Preferred Tool to assess Bleeding Risk
(R Pisters et al:Chest 2010;138:1093-1100)

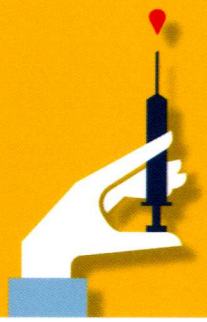
HAS-BLED RISK FACTORS	SCORE
Hypertension (>160 mm Hg systolic)	1
Abnormal renal (creatinine >200)	1
Abnormal Liver (bilirubin x 2, ALT x 3)	2
Stroke	1
Previous Bleeding	2
Labile INRs (TTR <60%)	1
Elderly Age >65 years	1
Drugs (NSAIDS/aspirin) Alcohol (8 drinks per week)	1+1

Use it to reduce bleeding risk, not to automatically 'trump' CHA2DS2-VASc

HAS-BLED Clinical Risk Estimate

Adapted from Pisters et al

HAS-BLED SCORE	NUMBER OF PATIENTS	NUMBER OF BLEEDING	BLEEDS PER 100 PATIENT YEARS
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	**12.50**
6	**2**	0	**0**
7	-	-	-
8	-	-	-



General Information

Atrial Fibrillation Related Stroke Prevention

When assessing atrial fibrillation stroke risk treat all types of AF whether recent, intermittent or permanent the same.

NICE defines poor INR control as 1 x > 8 or 2 x < 1.5 in the last 6 months: Investigate compliance & evaluate the risk/benefit of an alternative.

TTR (Time in Therapeutic Range) should be at least 65% (in the last 6 months).

If on aspirin for an acute MI or stent, stop it when 12 months from most recent cardiac event.

The older the patient, the higher the stroke risk and the greater the benefit from anticoagulation.

General Information

Atrial Fibrillation Related Stroke Prevention

Aspirin Monotherapy is no longer recommended.

Use an audit tool such as GRASP-AF or RAID-R to check on your quality of management.

If switching anticoagulants or stopping before surgery use the online interactive tool on www.thrombosiscanada.ca - it does it for you!

Consider an Echocardiogram as it may reveal LVSD or Mitral Valve Disease.

Valvular Heart Disease : Mitral Valve Stenosis, Mitral Valve (mechanical) Replacement and (recent) Mitral Repair were excluded from all NOAC trials - use warfarin.

Ensure patients are carrying an anticoagulant alert card.

Helping the Patient to Choose an Anticoagulant

There is a NICE Patient Decision Aid www.nice.org.uk/resource/CG180/pdf/c/cg180-atrial-fibrillation-update-patient-decision-aid with helpful 'smiley faces' charts

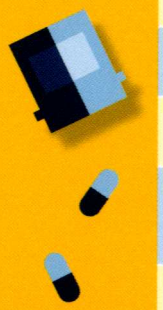
Allow a little time to make a decision - a few days at most and remind the patient that the decision can always be changed!

Note that Praxbind (Idarucizumab) - a reversal agent for Dabigatran is now licensed and reverses this drug in minutes. Andexanet Alpha for factor X's has completed phase III trials, so lack of an 'antidote' should no longer be a bar to prescribing NOACs.

'How often should I monitor renal function on a NOAC?' ***TOP TIP: Divide creatinine clearance by 10 = monthly frequency of monitoring***

Things to Discuss

Helping the Patient to Choose an Anticoagulant



How much do I wish to avoid a stroke?
DO NOT use aspirin.

How well do they work?
All work to reduce around 2/3 strokes.

How do I know the medicine is working?
Favours warfarin as clotting is monitored.

How often do I need to take tablets?
Once or twice daily options.

What happens if I miss a tablet?
Favours warfarin as NOACs have a short half-life and compliance is important.

Do I need regular blood tests?
All OACs require some monitoring: INR for VKA, renal function for NOAC.

... And how often?
Monitoring of renal function remains necessary with NOACs.

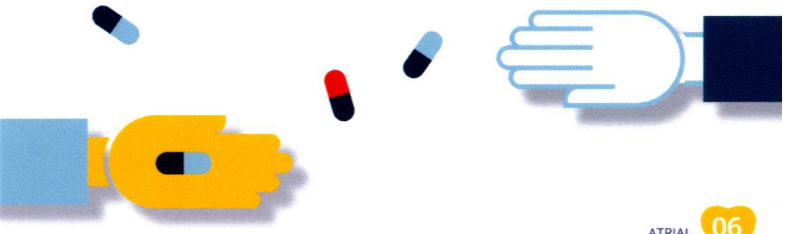
Do I need to watch my diet and drinking?
Favours NOAC as warfarin more affected by alcohol and dietary factors.

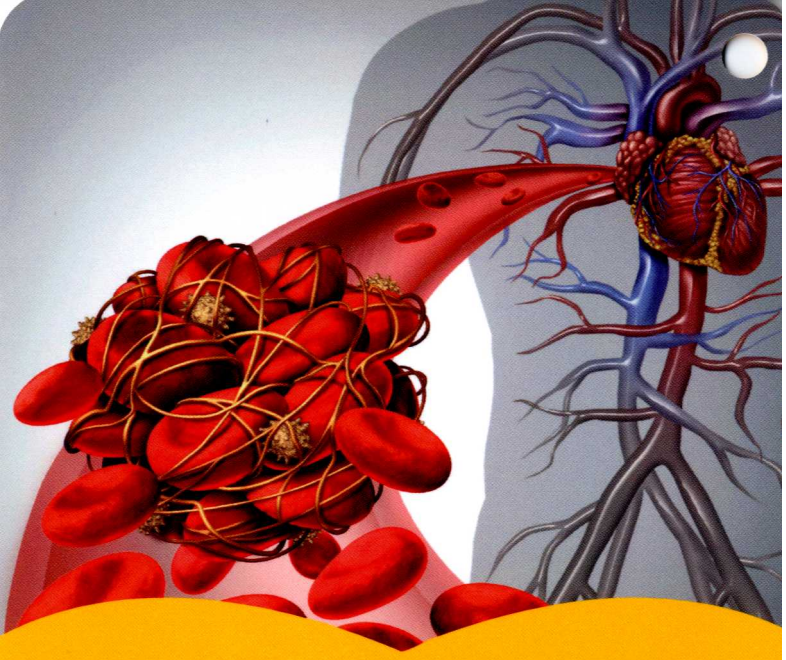
What would happen if I had bleeding?
Half-life of NOACs is short. Prothrombin Complex Concentrates exist to reverse warfarin. New Reversal Agents now available for NOACs.

Do they interact with my other medicines?
Favours NOAC.

Outcome of New Oral Anticoagulants vs Warfarin

TRIAL	MAJOR BLEED	ICH - BRAIN BLEED	ISCHAEMIC STROKE/ EMBOLISM	DEATH
DABIGATRAN 110 RE-LY TRIAL	*SUPERIOR*	*SUPERIOR*	*NON-INFERIOR*	*NON-INFERIOR*
DABIGATRAN 150 RE-LY TRIAL	*NON-INFERIOR*	*SUPERIOR*	*SUPERIOR*	*NON-INFERIOR*
RIVAROXABAN ROCKET-AF TRIAL	*(Similar) Rivaroxaban: More GI bleeds 3.2 vs 2.2% but less fatal bleeds on Rivaroxaban*	*SUPERIOR*	*NON-INFERIOR*	*NON-INFERIOR*
APIXABAN ARISTOTLE TRIAL	*SUPERIOR*	*SUPERIOR*	*SUPERIOR*	*SUPERIOR*
EDOXABAN (HIGH DOSE) ENGAGE-TIMI 48 TRIAL	*NON-INFERIOR*	*SUPERIOR*	*NON-INFERIOR*	*SUPERIOR*





Atrial fibrillation is the most common heart rhythm disturbance, affecting around one million people in the UK.

The view of the NECV Network/AHSN panel was to exercise caution in the elderly and groups that have not been well studied.

The study designs were different and the NOACs were not compared head to head.

The most AF related stroke reduction was seen with Dabigatran 150, but the necessity for good kidney function may limit its use. Dabigatran 110 showed similar efficacy to warfarin but with lower bleeding rates.

Rivaroxaban was trialled in higher risk patients - CHADS 3.4. This is a group which is consistently under-anticoagulated in the UK. It was given once daily in the trial and was non-inferior to warfarin. The higher bleeding rates reflected the higher risk population; many of the risks for stroke are also risks for bleeding. Though there was more GI bleeding with Rivaroxaban it was generally non-fatal.

Which New Oral Anticoagulant?

Apixaban showed mortality benefit in its trial vs. warfarin and the dose was reduced to 2.5mg in 2 of the following 3 criteria: 1. elderly > 80 years and 2. < 60Kg and 3. with renal impairment (creatinine = ≥ 133). The older and more renally impaired the patient, the greater the benefit over warfarin.

Edoxaban was trialled last of the NOACs in a large trial including moderate to high risk patients (CHADS 2.8). It achieved non inferiority for stroke/SEE prevention against well controlled warfarin (median TTR 68%) as well as a significantly lower bleeding risk.

In a meta-analysis by Ruff in the Lancet, the NOACs significantly reduced all-cause mortality compared to warfarin mainly driven by the large reduction in Intracranial Haemorrhage - about half that of warfarin. Though there was a slight increase in GI bleeding on NOACs compared to warfarin this was generally non-fatal (and this is despite the NOACs not having a specific 'antidote' at the time of analysis). These data showed a superiority in stroke reduction and embolic events of 19% compared to warfarin.

EHRA Guidance August 2015

There is no randomized study comparing VKA vs. NOAC in this setting, and there is no ideal combination fitting every patient.

The type and level of anticoagulation as well as SAPT (Single AntiPlatelet) vs. DAPT (Dual Antiplatelet) and its duration need to be highly personalized, based on atherothrombotic risk, cardioembolic risk, and bleeding risk.

Anticoagulants and Antiplatelets in IHD

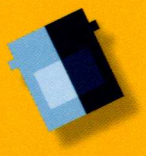
0-1 MONTH

All patients having had a stent or ACS will be usually recommended to have 'Triple Therapy' of OAC/aspirin/clopidogrel for the first month.

FROM 1-12 MONTHS

Depends on the procedure/type of stent/bleeding and thrombotic risk - seek local cardiological guidance.

AFTER 12 MONTHS

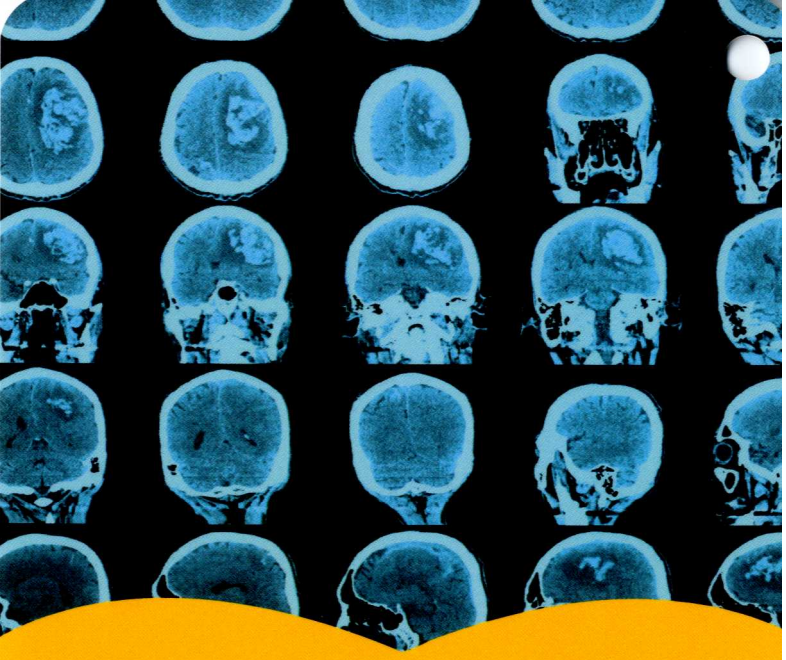


For all CAD patients with AF, the default is to step down to anticoagulation monotherapy, ie. Stopping Antiplatelet Therapy except for those with a very high risk for coronary events and an acceptably low bleeding risk.

Reference: http://europace.oxfordjournals.org/content/europace/early/2015/08/29/europace.euv309.full.pdf

GP Checklist

- [x] Rate - controlled to a ventricular rate of below 90?
- [x] Is there any heart failure that needs treating?
- [x] If recent onset refer to consider Cardioversion.
- [x] Risk stratified for stroke with CHA2DS2VASc.
- [x] Bleeding risk checked with HAS-BLED.
- [x] Discuss options with patient - offer all alternatives.
- [x] Don't wait to anticoagulate.
- [x] If using a NOAC is the kidney function good enough?
- [x] Issue alert card.
- [x] Arrange follow up.



AF affects about 7 in 100 people aged over 65 and it is usually asymptomatic. Effects of AF-related stroke are much more serious with 2 out of every 5 ending in death, another 2 going into an institution and only 1 going home.

Resources

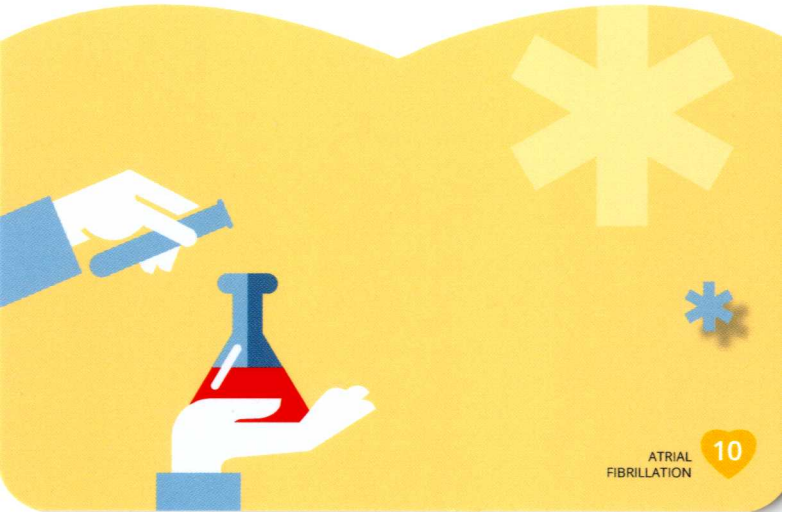
FOR PATIENTS

www.atrialfibrillation.org.uk/patient-information/treatments

www.stroke.org.uk/what-stroke/are-you-risk-stroke/atrial-fibrillation

www.bhf.org.uk

www.patient.co.uk



Resources

TRIALS

Dabigatran (RE-LY)
N Engl J Med 2009; 361:1139-1151 September 17, 2009
DOI: 10.1056/NEJMoa0905561

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N Engl J Med 2011; 365:981-992 September 15, 2011
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Edoxaban (Engage-Timi-48)
N Engl J Med 2013; 369:2093-2104 November 28, 2013
DOI: 10.1056/NEJMoa1310907

FOR DOCTORS

www.nice.org.uk (CG 180)

www.afibmatters.org/treatments

www.stroke.org.uk/take-action/atrial-fibrillation-af/information-professionals

www.thrombosiscanada.ca A useful interactive tool that tells you starting doses and what to do prior to different types of surgery and dental work.

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Appendix A - Trials

OUTCOMES (% PER YEAR)									
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban
	(n=6022)	(n=6076)	(n=6015)	(n=7133)	(n=7131)	(n=9081)	(n=9120)	7036	7035 (60mg)
		(RR, 95% CI;P value	RR, 95% CI;P value		RR, 95% CI;P value		RR, 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)	1.5	1.18 HR=0.79 (97.5% CI 0.63-0.99)p<0.001 for non inferiority HR=0.87 (97.5% CI 0.73 – 1.04) p=0.08 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)	1.25%	1.25% HR=1.00 (95%CI 0.83 – 1.19) p=0.97
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)	1.69%	1.49% HR=0.88 (95%CI 0.75-1.03) p<0.001 for superiority

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		(RR, 95% CI;P value	RR, 95% CI;P value		RR, 95% CI;P value		RR, 95% CI;P value		
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)	3.43%	2.75% HR=0.80 (95% CI 0.71-0.91) p<0.001 for superiority
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)	0.85%	0.39% HR=0.47 (95%CI 0.34-0.63) p<0.001 for superiority
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)						Not reported

Appendix B

SUMMARY OF THE CLINICAL TRIALS INVOLVING NOVEL ANTICOAGULANTS VS WARFARIN FOR STROKE PREVENTION IN NON-VALVULAR AF				
	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AFo	Apixaban (ARISTOTLE)	Edoxaban
DRUG CHARACTERISTICS				
Mechanism	**Oral direct**	Oral direct factor Xa inhibitor	**Oral direct factor Xa inhibitor**	Oral Direct Factor Xa Inhibitor
Bioavailability , %	**6**	60-80	**50**	62%
Time to peak levels, h	**3**	3	**3**	1-2 hrs
Half-life, h	**12-17**	5-13	**9-14**	10-14 hrs
Excretion	**80% renal**	2/3 liver, 1/3 renal	**25% renal, 75% faecal**	50% renal (<10%CYP)
Dose	**150 mg b.i.d.**	20 mg o.d.	**5 mg b.i.d.**	60mg
Dose in renal impairment	**110 mg b.i.d.**	15 mg o.d. (if CrCl 30-49 mL/min)	**2.5 mg b.i.d.**	30mg Use 30 mg in patients with low body weight < 60kg or concomitant use of the following PGP inhibitors:ciclosporin, dronedarone, erythromycin and ketoconazole.
Special considerations	**Intestinal absorption is pH-dependent and is reduced in patients taking proton pump inhibitors.**	Higher levels expected in patients with renal or hepatic failure.	-	-

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SUMMARY OF THE CLINICAL TRIALS INVOLVING NOVEL ANTICOAGULANTS VS WARFARIN FOR STROKE PREVENTION IN NON-VALVULAR AF				
	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AFo	Apixaban (ARISTOTLE)	Edoxaban
STUDY CHARACTERISTICS				
Study design	**Randomised, open-label**	Randomised, double-blind	**Randomised, double blind**	-
Number of patients	**18111**	14264	**18201**	-
Follow-up period, years	**2**	1.9	**1.8**	-
Randomised groups	**Dose-adjusted warfarin vs blinded doses of dabigatran (150 mg b.i.d., 110 mg b.i.d.)**	Dose-adjusted warfarin vs. rivaroxaban 20 mg o.d.	**Dose-adjusted warfarin vs. Apixaban 5 mg b.i.d.**	-
BASELINE PATIENT CHARACTERISTICS				
Age, years	**71.5 ± 8.7 (mean ± SD)**	73 (65-78 [median(inter quartile range)]	**70 (63-76) [median(inter quartile range)]**	-
Male sex %	**63.6**	61.3	**64.5**	-
CHADS (mean)	**2.1**	3.5	**2.1**	-

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NORTH EAST AND NORTH CUMBRIA

Stroke association

AFAssociation
www.afa.org.uk

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