ATRIAL FIBRILLATION

MANAGEMENT IN PRIMARY CARE

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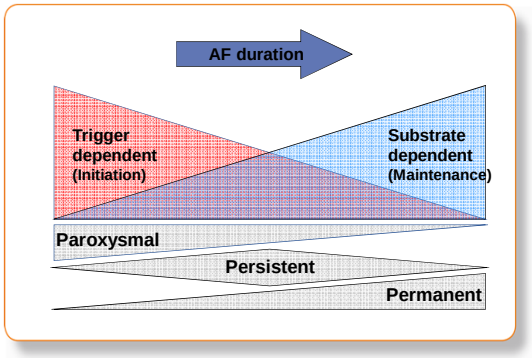
What are the facts?

- AF affects more than 1 million people in the UK.
- The lifetime risk in the forties, of developing AF is 1 in 4; the risk roughly doubles with every decade over the age of 55 yrs. AF is the 4th most important risk factor for stroke after HT, previous stroke/TIA and IHD.
- The Sentinel Stroke National Audit programme (SSNAP) August 2013 found that only 36% of patients admitted with stroke were on anticoagulants.
- AF increases the risk of stroke by about 5 times. Up to 40% of cryptogenic strokes are believed to be due to undiagnosed PAF and latest advice is 30 day ambulatory monitoring after TIA/stroke
- It is estimated that 4500 strokes per year can be prevented and 3000 lives saved if everyone with AF was appropriately managed

AF is a Progressive Disease



AF=atrial fibrillation
Khan IA, et al. *Int J Cardiol* 2003; **87**: 301–7

Management of AF

- Clinical assessment including bloods and echocardiogram
- Control of rate and/or rhythm
- Reducing the risk of stroke associated with AF
- *Incorporating the latest evidence and NICE guidance*

Rate control - NICE

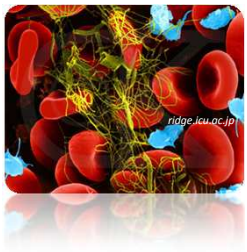
1. Beta–blocker or diltiazem as initial monotherapy
2. Digoxin monotherapy with non-paroxysmal AF only if individual is sedentary or takes little exercise
3. If patient still symptomatic or poor ventricular rate control combine 2 out of betablocker, diltiazem or digoxin
4. Avoid using anti-arrhythmics for rate control unless initiated in hospital

Referral for specialised management

- Acute symptomatic AF should be referred within 48 hours for consideration of cardioversion
- Patients with chronic AF who are **symptomatic** inspite of medical treatment
- Clinical assessment or echocardiography indicating underlying structural or functional disease eg heart failure
- If the GP feels a specialist opinion is indicated
- If acute AF presents after 48 hours, patient should be rate controlled (eg Bisoprolol) and anticoagulated for atleast 3 weeks before cardioversion can be considered.

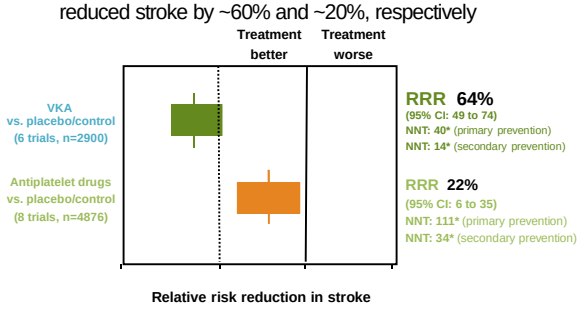
Not all clots are the same

- Thrombi in patients with AF are predominately fibrin-rich
- Thrombi in coronary artery disease (CAD) tend to be platelet-rich
- Anticoagulants reduce the conversion of fibrinogen to fibrin
- Aspirin and other antiplatelets, inhibit aggregation of thrombi caused by CAD, but do not impact upon fibrin production



Lip GYH. *Nature Reviews Cardiology* 2011;8:602–606

In historical trials in AF patients, VKA and antiplatelet agents reduced stroke by ~60% and ~20%, respectively



RRR 64%
(95% CI: 49 to 74)
NNT: 40* (primary prevention)
NNT: 14* (secondary prevention)

RRR 22%
(95% CI: 6 to 35)
NNT: 111* (primary prevention)
NNT: 34* (secondary prevention)

*NNT for one year to prevent one stroke
**If data confined to ASA, the RRR is 19% (95% CI: -1 to 35, NS)

Hart et al. Ann Intern Med 2007;146:857–67.

Absolute stroke risk vs absolute bleeding risk

- Online stroke risk calculator @ www.preventaf-strokecrisis.org/calculator/
- Qbleed online algorithm which calculates risk of an upper GI bleed or intracranial bleed with or without anticoagulation
  - Original algorithm built in comparison with warfarin and not NOACs

CHA_2DS_2-VASc score

Congestive Heart Failure/ LVD	1	1	0.6-2.0%
Hypertension	1	2	2.2-3.7%
Age ≥ 75 years	2	3	3.2-5.9%
Diabetes mellitus	1	4	4.8-9.3%
Stroke/TIA/TE	2	5	7.2-15.3%
Vascular disease (previous MI, PAD or aortic plaque)	1	6	9.7-19.7%
Age between 65 and 74 years	1	7	11.2-21.5%
Sc - Sex category - Female	1	8	10.8-22.4%

HIGH risk = a score of 2 or more (antithrombotic therapy)
Score of 1 recommends anticoagulant therapy in males..
Consider a risk of bleeding assessment such as the **HAS-BLED** score before anticoagulation.

HAS-BLED score- Bleeding risk of oral anticoagulation in AF

Hypertension (Systolic ≥ 160mmHg)	1
Abnormal renal/liver function	1or2
Stroke in past	1
Bleeding tendency or predisposition	1
Labile INRs	1
Elderly (≥ 65yrs)	1
Drugs (aspirin or NSAIDS) or alcohol	1or2

A score of 3 or more indicates increased one year bleed risk on anticoagulation sufficient to justify caution or more regular review.

Advantages of new oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular AF

- predictable effect without need for monitoring
- fewer food and drug interactions
- more predictable half-life/elimination
- improved efficacy/safety ratio

NOACs approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Action	Direct thrombin inhibitor	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 III clinical trial	RE-LY [1]	ARISTOTLE [2] AVERROES [3]	ENGAGE-AF [4]	ROCKET-AF [5]

* not yet approved by EMA

1. Connolly et al, N Engl J Med 2009; 361:1139-51
2. Granger et al, N Engl J Med 2011; 365:981-92
3. Connolly et al, N Engl J Med 2011; 364:806-17
4. Ruff et al, Am Heart J 2010; 160:635-41
5. Patel et al, N Engl J Med 2011;365:883-91

Absorption and metabolism of NOAC

	Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
Bioavailability	3-7%	50%	62%	66% (w/o food) ~100% with food
Prodrug	yes	no	no	no
Clearance: non-renal/renal of adsorbed dose if normal renal function	20%/80%	73%/27%	50%/50%	65%/35%
Liver metabolism: CYP3A4	no	yes (elimination; minor CYP3A4)	minimal (<4% of elimination)	yes (elimination)
Absorption with food	no effect	no effect	6-22% more	+39%
Intake with food?	no	no	no official recommendation yet	mandatory
Absorption with H2B/PPI	plasma level -12 to -30%	no effect	no effect	no effect
Asian ethnicity	plasma level +25%	no effect	no effect	no effect
GI tolerability	dyspepsia 5-10%	no problem	no problem	no problem
Elimination half-life	12-17h	12h	9-11h	5-9h (young)/11-13h (elderly)

* not approved yet

Possible drug-drug interactions – Effect on NOAC plasma levels part 1

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Possible drug-drug interactions – Effect on NOAC plasma levels part 2

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4				+42%
Cyclosporin; tacrolimus	P-gp				+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%		no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4		strong increase		up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12-30%		no effect	no effect

Red – contraindicated; orange – reduce dose; yellow – consider dose reduction if another yellow factor present; hatching – no data available; recommendation made from pharmacokinetic considerations

Practical start-up and follow-up scheme for patients on NOACs

- Risk/benefit analysis: is a NOAC indicated?
- When choosing a NOAC, consider co-medications taken by patient.
- Consider co-medications such as PPI to reduce risk for gastro-intestinal bleeding.
- Carry information card: generic card could serve for all NOACs.
- Need to educate patient on importance of strict adherence to regimen – discontinuation is dangerous.

Need for structured follow-up

- All NOACs are anticoagulants and hence can cause serious bleeding.
- All NOACs have some drug-drug interactions (DDIs).
- AF population is a fragile patient population.
- Patients should return for ongoing review according to a predetermined schedule.
- Follow-up can be undertaken by specialist or GP with experience in the field and/or appropriate secondary care physicians.
- Nurse co-ordinated AF clinics may be used. [1]

1. Berti et al, Eur Heart J, 2013 (Epub ahead of print)

www.escardio.org/EHRA

Follow-up: considerations

- Renal function: impaired renal function increases plasma levels and hence anticoagulant effect of all NOACs, especially dabigatran. Dose reduction may be indicated.
- Minor bleeding: most is temporary and classified as 'nuisance'. Discontinuation or dose reduction should not be considered unless frequent and impacting on patient's QoL.

www.escardio.org/EHRA

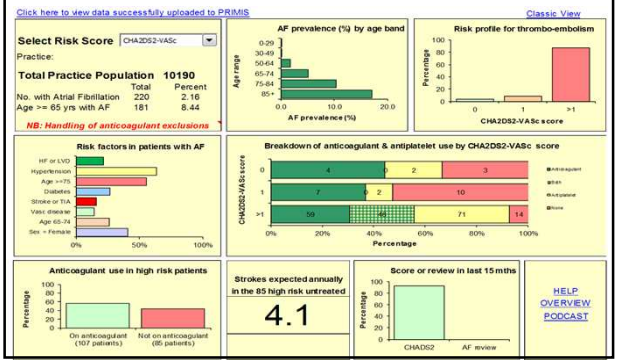
Current challenges in management of AF

- Identification of AF in asymptomatic individuals
  - Opportunistic pulse checks
  - Targeted pulse checks in high risk cohorts
  - Encouraging patients to self-diagnose eg AliveCor
- Making a shared decision about oral anticoagulation
  - Ensuring clinician training and confidence
  - Ensuring shared decision making with patient
- Ensure adequate anticoagulation
  - Ensuring appropriate time in therapeutic range for warfarin patients
  - Use of direct oral anticoagulants and establishing safe monitoring systems

Strategies to employ

- Individual approach - making each contact count
- Population approach - employing strategies to improve detection of AF and increasing anticoagulation rates in this cohort

GRASP – AF Dashboard



Summary

- NOACs have similar efficacy to warfarin in preventing strokes and thromboembolic phenomena, esp if TTR with warfarin is 65% or more.
- Real world AF data (registry) shows the main issue is still underuse of oral anticoagulants in high risk patients with AF; overall the pattern of benefits with the NOACs mirror the original trials
- NOACs have lower rates of intracerebral bleeds compared to warfarin, the effects more prominent in non-Europeans, and in patients with previous CVA or TIA
- NNTB for ICH for NOACs overall is 271, in European population 337 and in non Europeans 232.