Screening, Diagnosis and Management of Atrial Fibrillation

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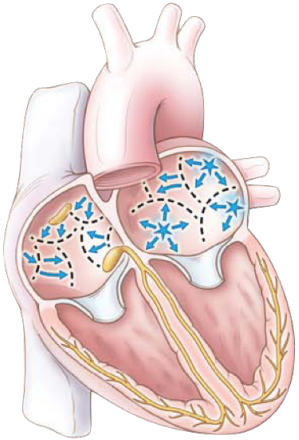
Why prioritise AF in primary care?

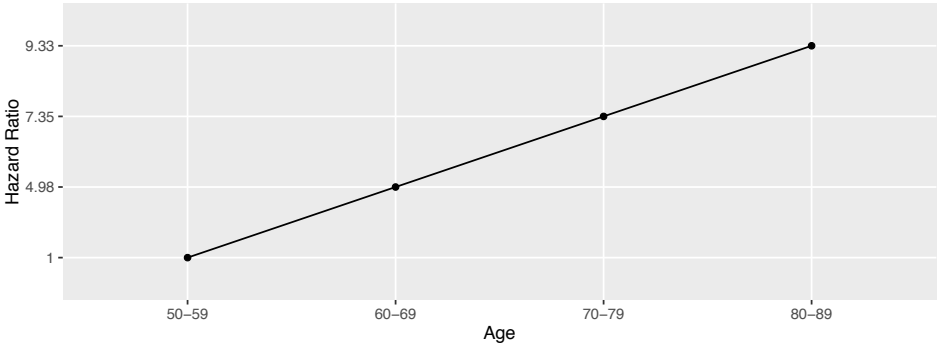


- Commonest arrhythmia
- Significant risk of stroke and symptoms

Why prioritise AF in primary care?

- Very common: lifetime risk for AF at >40 yrs is 1 in 4
- 2% of total adult population
- >1,000,000 cases diagnosed
- >100,000 new AF cases yr in UK
- Prevalence is expected to double over the next twenty five years

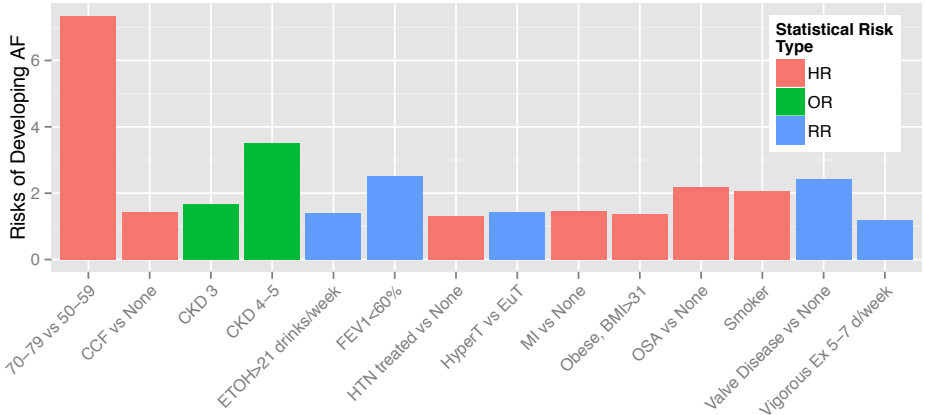
Age as Risk Factor for AF



Overview of Major Risk Factors for AF

Risk Factor	Risk Type	Risk Value
Age 70-79 vs 50-59	HR	7.35
CKD 4-5	OR	3.52
COPD, FEV1<60%	RR	2.53
Valvular Heart Disease vs None	RR	2.42
OSA vs None	HR	2.18
Current Smoker	HR	2.05
CKD 3	OR	1.68
Myocardial Infarction vs None	HR	1.46
Heart Failure vs None	HR	1.43
Hyperthyroid vs Euthyroid	RR	1.42
Alcohol Consumption> 21 drinks/week	RR	1.39
Obese, BMI>31	HR	1.37
Hypertension treated vs None	HR	1.32
Habitual Vigorous Exercise 5-7 days/week	RR	1.20

Graph of All Risks



Risk of Stroke[1]

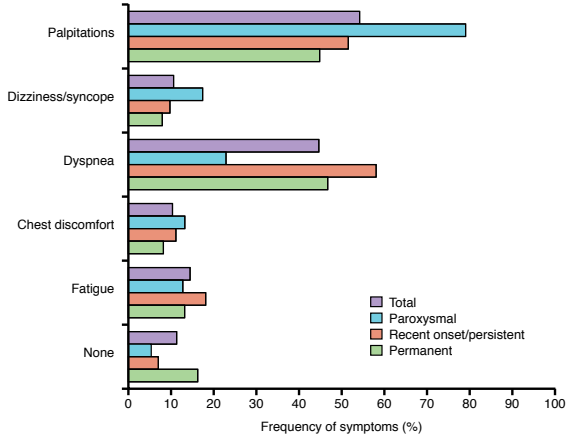
SR **AF**

Stroke risk x 5

Risk of Stroke

- AF increases risk of stroke x5
- AF relates to approx 20–30% of strokes
- Devastating consequences
- AF related stroke approx 50% 1 yr mortality[2]
- AF strokes more severe
  - Longer in hospital, greater disability, higher risk of death
- Preventable with anticoagulation
- Anticoagulation prescribing can be improved

Symptoms[3]

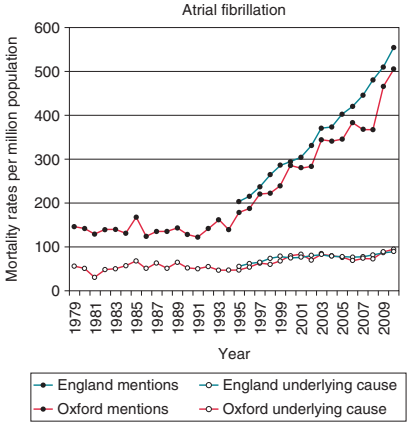

Palpitations
Dizziness/syncope
Dyspnea
Chest discomfort
Fatigue
None
Total
Paroxysmal
Recent onset/persistent
Permanent
0
10
20
30
40
50
60
70
80
90
100
Frequency of symptoms (%)

Disability-adjusted life years (DALYs) With AF[4]

	All ages DALYs (thousands)			DALYs (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
Rheumatic heart disease	14 418 (13 170–16 236)	10 150 (9 058–11 308)	−29·6	272 (248–306)	147 (131–164)	−45·8
Ischaemic heart disease	100 473 (96 503–108 966)	129 820 (119 174–138 044)	29·2	1895 (1820–2055)	1884 (1730–2004)	−0·6
Cerebrovascular disease	86 010 (81 022–94 811)	102 232 (90 428–107 989)	18·9	1622 (1528–1788)	1484 (1312–1567)	−8·5
Ischaemic stroke	32 128 (29 567–36 615)	39 389 (36 906–45 504)	22·6	606 (558–691)	572 (536–660)	−5·7
Haemorrhagic and other non-ischaemic stroke	53 882 (45 237–63 351)	62 843 (54 386–72 540)	16·6	1016 (853–1195)	912 (789–1053)	−10·3
Hypertensive heart disease	11 152 (9216–13 691)	15 324 (12 835–18 433)	37·4	210 (174–258)	222 (186–268)	5·7
Cardiomyopathy and myocarditis	9148 (7463–10 970)	11 151 (9759–12 882)	21·9	173 (141–207)	162 (142–187)	−6·2
Atrial fibrillation and flutter	1854 (1377–2429)	3598 (2756–4578)	94·1	35 (26–46)	52 (40–66)	49·3
Aortic aneurysm	2349 (1629–3220)	3163 (2280–4235)	34·6	44 (31–61)	46 (33–61)	3·6
Peripheral vascular disease	505 (342–748)	995 (703–1445)	97·1	10 (6–14)	14 (10–21)	51·7
Endocarditis	1489 (1215–1828)	1582 (1245–1839)	6·2	28 (23–34)	23 (18–27)	−18·3
Other cardiovascular and circulatory diseases	13 266 (11 425–15 212)	17 021 (15 191–19 188)	28·3	250 (216–287)	247 (220–278)	−1·3

49·3

Mortality Rates and Atrial Fibrillation in UK[5]

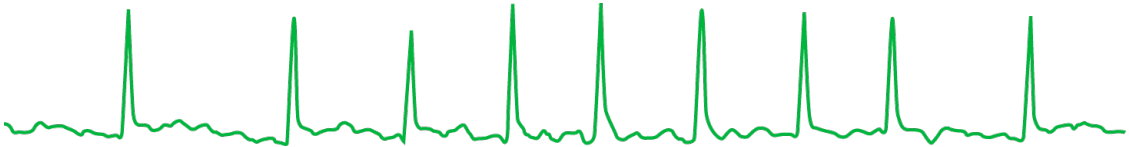


Screening - NICE

- Perform manual pulse palpation in people with:
  - palps/SOB/CP/syncope/dizzy
- In patients with risk factors:
  - Hypertension, diabetes and IHD
- Opportunistic assessment of such patients for the presence of AF may be prudent

AF Diagnosis

- Must be documented
- ECG/Holter/Other
- Absolutely **irregular irregular** RR intervals
- No distinct P waves on the ECG



AF Classification

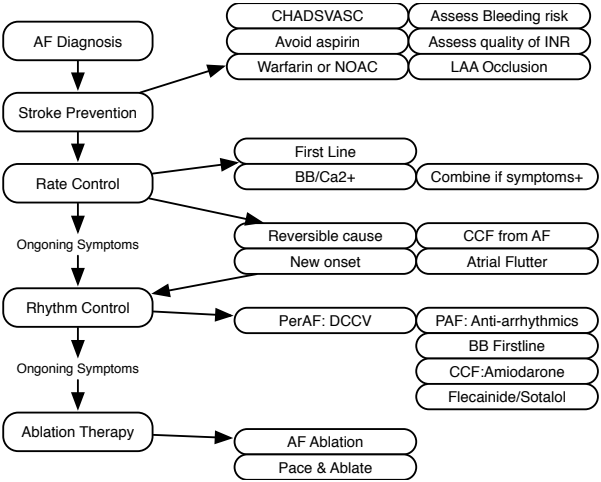
- Paroxysmal - AF stops spontaneously < 7 day
- Persistent - continuous AF > 7 days
- Long standing persistent - continuous AF > 1yr
- Permanent - AF accepted by patient & Dr

Use of Holter and Prolonged Monitoring

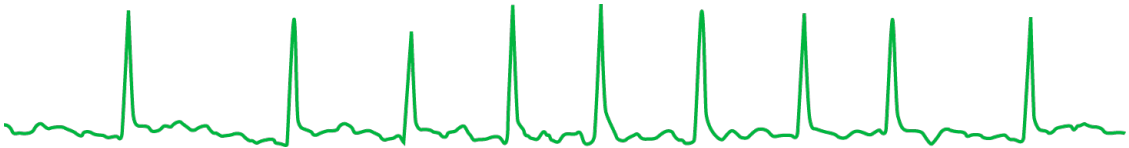
Echocardiography

- High risk or a suspicion of underlying structural/functional heart disease
- Rhythm-control strategy is being considered
- Refinement of clinical risk stratification for antithrombotic therapy is needed

AF Management Overview - NICE Pathway



Rate Control



Rate Control in AF

- Rate control is an integral therapy in AF
- Often sufficient to improve AF-related symptoms.
- Little robust evidence exists to inform the best type of rate control
- Pharmacological rate control can be achieved for acute or long-term rate control with
  - Beta-blockers
  - Digoxin
  - Calcium channel blockers: Diltiazem and Verapamil
  - Or combination therapy
- Some antiarrhythmics have rate-limiting effect
  - Amiodarone
  - Dronedarone
  - Sotalol
  - To some extent propafenone
  - Only used for rhythm control therapy

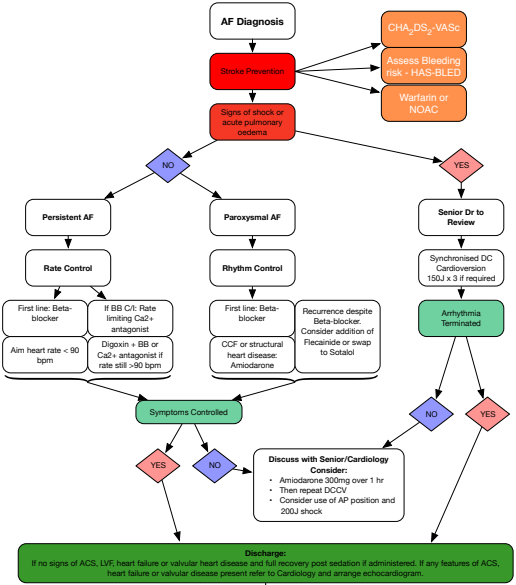
Rate Control - NICE Guidance

- Offer rate control as the first line strategy for all people with AF
- Initial monotherapy BB or Calcium channel blocker
- Digoxin only for non-paroxysmal AF in sedentary patients
- Add second agent if required for heart rate control

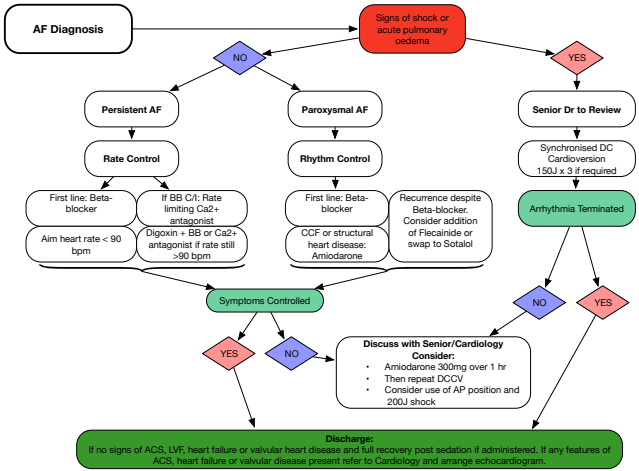
Rate control Exceptions - NICE Guidance

- AF with reversible cause
- Heart failure primarily caused by AF
- New-onset AF
- Atrial Flutter (suitable for ablation)
- Rhythm control more suitable based on clinical judgement

Pathway for New AF Diagnosis



Pathway for NEW AF Diagnosis



Acute Rate Control - Exclude Underlying Factors

- Exclude underlying causes of elevated heart rate
  - Infection
  - Endocrine imbalance
  - Anaemia
  - Pulmonary embolism

Drug Choice For Acute Rhythm Control

- For acute control
  - Beta-blockers
  - Diltiazem/Verapamil prefered to digoxin
    - Rapid onset
    - Effective with high sympathetic tone
- Combination therapy may be required
- BB and digoxin better than Ca^{2+} antagonists in HFrEF
- Ca^{2+} can be -ve inotropic when EF<40%
- Amiodarone in critically ill patients or in severely reduced LVEF when excess HR = BP instability
- Urgent DCCV considered in unstable patients

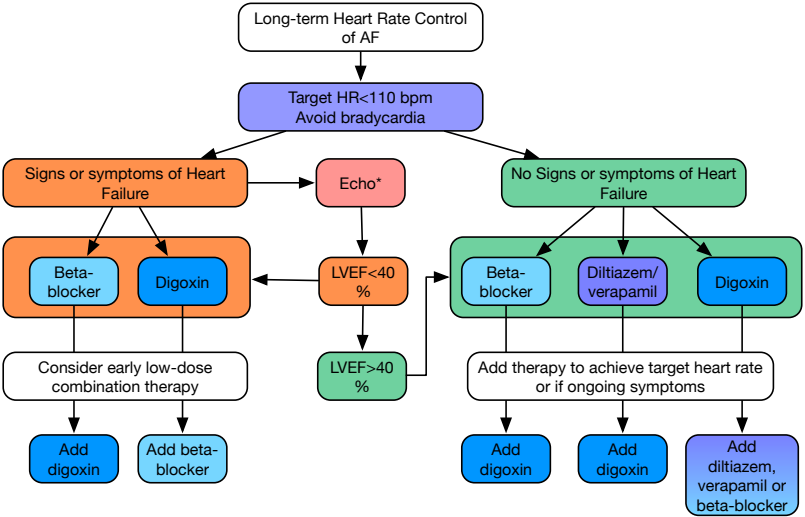
Acute IV Rate Control

Drug	IV Dose
Metoprolol	2.5–10 mg iv bolus (repeat as required)
Esmolol	0.5 mg/Kg iv bolus over 1 min; then 0.05–0.25 mg/kg/min
Verapamil	2.5–10 mg iv bolus (repeat as required)
Digoxin	0.5 mg iv bolus (0.75–1.5 mg over 24 hours in divided doses
Amiodarone	300 mg iv bolus in 250 ml 5% dextrose over 30–60 mins (ideally via central line)

Long-term Rate Control Drugs

- Equipoise for different rate control agents in AF
- Choice of BB, diltiazem/verapamil, digoxin, or combination
- Individual basis, consider patient characteristics/preferences
- All have the potential for adverse effects
- Treat with a low dose and up-titrate to achieve symptom improvement
- Achieving a HR <110 b.p.m. often requires combination therapy

Long-term Rate Control Flow Chart



Beta-blockers for Long-term Rate Control

- BB monotherapy often 1st line
- Better acute HR control than digoxin
- Symptom and functional benefits
- Lack of harm in studies

Long-term Use of Ca^{2+} For Rate Control

- Verapamil or diltiazem provide reasonable rate control
- Avoid in patients with HFrEF
- Improve arrhythmia related symptoms
- Alternative choice for patients that suffer reduced exercise capacity with BBs

Digoxin

- Randomized Digitalis Investigation Group (DIG) trial
  - Digoxin had no effect on mortality compared to placebo in HFrEF in SR
  - But reduced hospital admissions
- No head-to-head RCTs of digoxin in AF patients
  - Observational studies have associated digoxin with excess mortality
  - Association is likely due to selection and prescription biases rather than harm caused by digoxin
- Comparisons with other rate control therapies
  - are based on small, short-duration studies
  - identify no or marginal differences in exercise capacity, quality of life, or LVEF compared to digoxin.
  - Lower doses of digoxin (<250 mcg once daily), corresponding to serum digoxin levels of 0.5–0.9 ng/mL, may be associated with better prognosis

Amiodarone

- Amiodarone can be useful for rate control as a last resort.
- Wide array of extracardiac adverse effects associated with amiodarone renders it a reserve agent
- In patients whose heart rate cannot be controlled with combination therapy (e.g. beta-blocker or verapamil/diltiazem combined with digoxin).

Long-term Rate Control

Drug	Oral Dose
Bisoprolol	1.25–20 mg od or split
Carvedilol	3.125–50 mg bd
Metoprolol	100–200 mg total daily dose
Nebivolol	2.5–10 mg od or split
Diltiazem	60 mg tds up to 120 mg tds (total max daily dose 360 mg), modified release 120–360 mg od.
Verapamil	40–120 mg tds (120–480 mg od modified release
Digoxin	0.0625–0.25 mg daily dose
Amiodarone	200 mg od

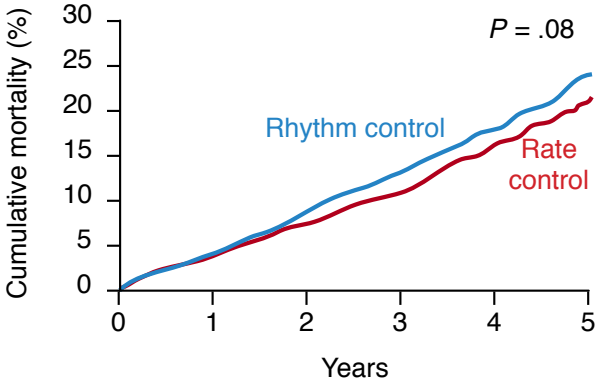
Rate Control Drug Side-Effects

Drug Class	Adverse Symptoms and Effects
Beta-blockers	Lethargy, headache, peripheral oedema, upper respiratory tract symptoms, GI upset and dizziness. Bradycardia, AV block and hypotension.
Ca^{2+} Channel Blockers	Dizziness, malaise, lethargy, headache, hot flushes, GI upset and oedema. Bradycardia, AV block and hypotension
Digoxin	GI upset, dizziness, blurred vision, headache and rash. In toxic states (serum levels >2 ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with co-existent hypokalaemia.
Amiodarone	Hypotension, bradycardia, nausea, QT prolongation, pulmonary toxicity, skin discolouration, thyroid dysfunction, corneal deposits and cutaneous reaction with extravasation.

Rate Control Drug Side-Effects Additional Notes

Drug Class	Adverse Effects Notes
Beta-blockers	Bronchospasm is rare in cases of asthma, recommend beta-1 selective agents (avoid carvedilol). Contra-indicated in acute cardiac failure and a history of severe bronchospasm.
Ca Channel Blockers	Use with caution in combination with beta-blockers. Reduce dose with hepatic impairment and start with smaller dose in renal impairment. Contra-indicated in LV failure with pulmonary congestion or LVEF <40%.
Digoxin	High levels associated with increased risk of death. Check renal function and adapt dose in patients with CKD. Contra-indicated in patients with accessory pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow tract obstruction.
Amiodarone	Suggested as adjunctive therapy in patients where heart rate control cannot be achieved using combination therapy.

AFFIRM Study[6]



When to Use Rhythm Control in AF

- Rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy

Rhythm Control in AF

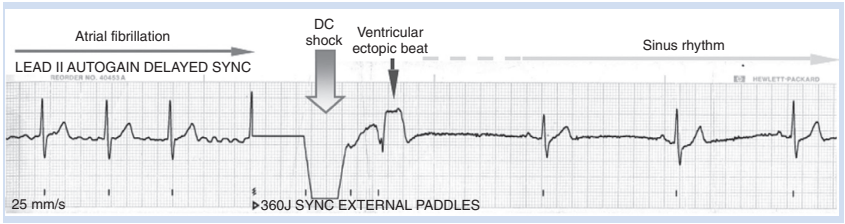
- Antiarrhythmics double the rate of sinus rhythm compared to placebo[7–11]
- Catheter ablation or combination therapy is often effective when antiarrhythmic drugs fail[12–15]

Options for Rhythm Control

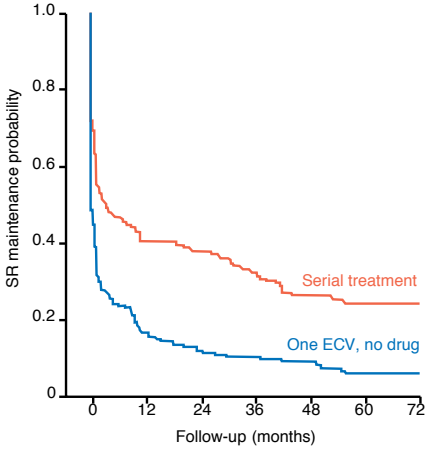
- Acute restoration
  - Flecainide or amiodarone IV or DCCV
- Pill in Pocket
  - Flecainide
- DCCV
- Daily therapy
  - Flecainide
  - Sotalol
  - Amiodarone

Electrical Cardioversion

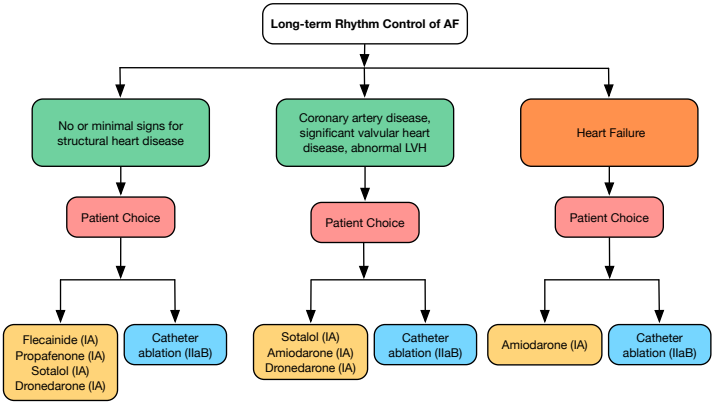
- Consider amiodarone for 4 weeks before and up to 12 months after



DCCV Recurrence



Rhythm Control Therapy Choices



Who to Refer

- NICE reccomends
  - Refer people promptly
  - At any stage
  - If treatment fails to control the symptoms of AF
- Also consider referring
  - Patients with difficult anticoagulation managment

Take a break

Extra Slides...

Antiplatelets and Anticoagulation Combinations in AF — Common Problem

- Approximately 15% of AF patients have a history of myocardial infarction
  - in contemporary trials[16]
  - registries[17,18]
- 5-15% AF patients will have PCI with stents during their lives

Combination therapy with oral anticoagulants and antiplatelets

- This scenario requires careful consideration of antithrombotic therapy
- Balancing bleeding risk, stroke risk, and risk of acute coronary syndromes (ACS)[19]
- Co-prescription of OAC with antiplatelet therapy, in particular triple therapy, increases the absolute risk of major haemorrhage.[20–22]

Bleeding Problems

- Compared with oral anticoagulation therapy alone
- The addition of DAPT to OAC therapy
- Results in at least a two- to threefold increase in bleeding complications[17,22–24]

Meta-Analysis ACS and NOACs

- Meta-analysis involving 30 866 patients[25]
- Recent ACS
- Evaluated the effects of adding NOAC therapy
  - to single (4,135 patients) or
  - dual (26,731 patients) antiplatelet therapy[25].
- Addition of a NOAC increased the bleeding risk by 79–134%
- while reducing recurrent ischaemic events marginally in patients without AF.

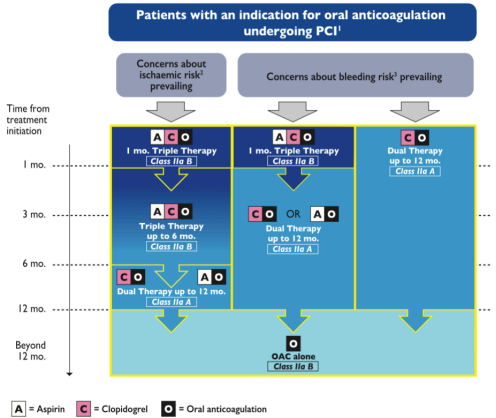
Recommendation OAC and antiplatelets in stable CAD

- OAC monotherapy
- Not combination therapy with antiplatelets
- Recommended in AF patients with stable CAD
- Without an ACS and/or coronary intervention in the previous 12 months.

Recommendation OAC and antiplatelets in ACS

- In patients treated for ACS
- And in those receiving a coronary stent
- Short-term triple combination therapy of OAC, clopidogrel, and aspirin seems warranted

Recommendation for OAC and Patients with PCI



Balance of Bleeding versus Risk of OAC and IHD

Table 5 High-risk features of stent-driven recurrent ischaemic events

• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

Table 6 Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

Class of Recommendations OAC and Antiplatelets with PCI

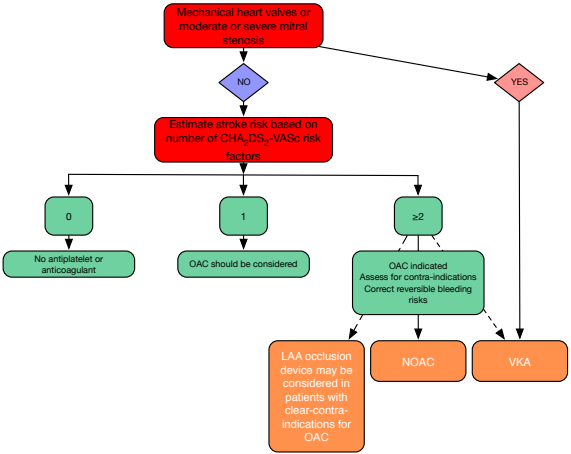
Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

Recommendations	Class[a]	Level[b]
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel, and OAC should be considered for 1 month, irrespective of the type of stent used.[195]	IIa	B
Triple therapy with aspirin, clopidogrel, and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk.[195]	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.[191,193]	IIa	A
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.[198]	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.[193,195]	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered.[c]	IIa	C
When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d.[191]	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

Stroke prevention therapy in AF patients

- OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life[26,27]
- Net clinical benefit is almost universal
- Exception of patients at very low stroke risk
- Despite this evidence
  - Underuse/premature termination of OAC is common

Stroke Prevention in AF Initial Steps



CHA_2DS_2-VASc of 1 in men and 2 in women

- Strong evidence in patients with CHA_2DS_2-VASc risk score $\geq$2 in men, and $\geq$3 in women
  - Benefit from OAC
- Growing evidence stroke risk in patients with one clinical risk factor
- CHA_2DS_2-VASc of 1 for men, and 2 for women
- Relies largely on observed stroke rates in patients not receiving OAC
  - In many of these patients, anticoagulation seems to provide a clinical benefit[28–31]
- OAC should be considered for men with a CHA_2DS_2-VASc score of 1 and women with a score of 2
- Balancing the expected stroke reduction, bleeding risk, and patient preference
- Age ($\geq$65 years) conveys a relatively high and continuously increasing stroke risk

Clinical risk scores for bleeding

- Stroke and bleeding risk factors overlap
- High bleeding risk score should generally not result in withholding OAC
- Rather, bleeding risk factors should be identified and treatable factors corrected
  - HTN
  - Anti-platelets
  - NSAIDS
  - Alcohol
  - Anaemia

CHA_2DS_2-VASc Points Scoring

Assess Risk of Stroke in Non-valvular AF and Atrial flutter using CHA_2DS_2-VASc Score.

Category	Score
Cardiac Failure/LV dysfunction	1
Hypertension	1
Age≥75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (IHD,PVD,Aortic)	1
Age 65-74	1
Sex category (female gender)	1
Maximum score	9

Note that heart failure refers to moderate to severe left ventricular systolic dysfunction, or recently decompensated heart failure requiring hospital admission, regardless of ejection fraction. Women who have no other risk factors (i.e. women who are < 65 years with lone AF) should also be regarded as truly low risk and treated as though they have a CHA_2DS_2-VASc score of 0.

CHA_2DS_2-VASc Risk

CHA_2DS_2-VASc Score and Annual Risk of Stroke

Cumulative Score	Adjusted stroke rate (% per year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

HAS-BLED Scoring System

HAS-BLED Scoring for Risk of Major Bleeding with Oral Anticoagulation.

Category	Score
Hypertension[1]	1
Abnormal renal[2] and liver function[3] (1 point each)	1 or 2
Stroke	2
Bleeding[4]	1
Labile INRs[5]	1
Elderley[6]	1
Drugs[7] or alcohol[8] (1 point each)	1

1. Systolic BP >160 mmHg
2. Chronic dialysis, transplantation, Creat>200 µmol/l
3. Bilirubin >2 x normal and AST/ALT >3 x normal
4. Previous bleeding history and/or predisposition to bleeding
5. Time in therapeutic range <60%
6. Age >65 years
7. Concomitant use of drugs such as aspirin and NSAIDs
8. Alcohol consumption >8 u/week

HAS-BLED Risks

HAS-BLED Score and Annual Risk of Major Bleed.

Cumulative HAS-BLED Score	Risk of Major Bleed, %
0	1.13
1	1.02
2	1.88
3	3.72
4	8.70
5	12.5

Stroke Prevention VKAs

- VKA therapy reduces
  - risk of stroke by two-thirds
  - mortality by one-quarter compared with control (aspirin or no therapy)[26]
- VKAs, when delivered with adequate (TTR),
  - are effective for stroke prevention in AF patients.
- VKAs only treatment established safety in AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis[32]

Limitations of VKAs

- Use of VKAs is limited by the narrow therapeutic interval
- Necessitating frequent monitoring and dose adjustments
- Clinical parameters can help identify patients likely to achieve target TTR on VKA therapy[33]
  - Summarised in the SAMe-TT_2R_2 score

Non-VKAs (NOACs)

- Direct thrombin inhibitor dabigatran
- Factor Xa inhibitors apixaban, edoxaban, and rivaroxaban
- Alternatives to VKAs for stroke prevention in AF
- Use in clinical practice is increasing rapidly[34]
- All NOACs have a predictable effect (onset and offset)
- Without need for regular anticoagulation monitoring

Apixaban

- ARISTOTLE (Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation) trial[35]
- Apixaban 5 mg twice daily
- Reduced stroke or systemic embolism by 21% compared with warfarin
- A 31% reduction in major bleeding
- An 11% reduction in all-cause mortality
- All statistically significant
- Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on apixaban
- Rates of GI bleeding were similar between the two treatment arms[36]

Dabigatran

- RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study,[37,38]
- Dabigatran 150 mg twice daily
- Reduced stroke and systemic embolism by 35% compared with warfarin
- Reduced ischaemic stroke by 24%
- Vascular mortality by 12%
- Without significant difference in major bleeding events
- Dabigatran 110 mg twice daily was non-inferior to warfarin
  - For prevention of stroke and systemic embolism
  - With 20% fewer major bleeding events
- Dabigatran 150 mg twice daily significantly while gastrointestinal bleeding was significantly increased by 50%

Edoxaban

- ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48) trial[39]
- Edoxaban 60 mg once daily
  - was non-inferior to warfarin
  - On-treatment analysis, significantly reduced stroke or systemic embolism by 21%
  - significantly reduced major bleeding events by 20% compared with warfarin
  - Cardiovascular death was reduced in patients
- Only the higher dose regimen has been approved for stroke prevention in AF

Rivaroxaban

- ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial[40]
- Rivaroxaban 20 mg once daily or VKA
- 15 mg daily for those with estimated CrCl 30–49 mL/min
- Rivaroxaban non-inferior to warfarin for prevention of stroke/embolism in the ITT analysis
- On-treatment analysis 21% reduction in stroke/embolism compared to VKA
- Did not reduce the rates of mortality, ischaemic stroke, or major bleeding compared to VKA
- Increase in GI bleeding events
- Significant reduction in haemorrhagic stroke and intracranial haemorrhage
- Comparable event rates have been reported in post- authorization analyses[41,42]

Non-vitamin K antagonist oral anticoagulants or vitamin K antagonists

- Both VKAs and NOACs are effective for the prevention of stroke in AF
- A meta-analysis[27]
  - 42,411 patients receiving a NOAC
  - 29,272 receiving warfarin
- NOACs significantly reduced stroke/embolic events by 19% vs warfarin (RR 0.81; 95% CI 0.73–0.91; P<0.0001)
  - Driven by reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; P<0.0001)
- Mortality was 10% lower in patients randomized to NOACs (RR 0.90; 95% CI 0.85–0.95; P<0.0003)
- Intracranial haemorrhage halved (RR 0.48; 95% CI 0.39–0.59; P , 0.0001)
- GI bleeding events more frequent (RR 1.25; 95% CI 1.01–1.55; P<0.04)

Meta-analysis Stroke or Systemic Embolism

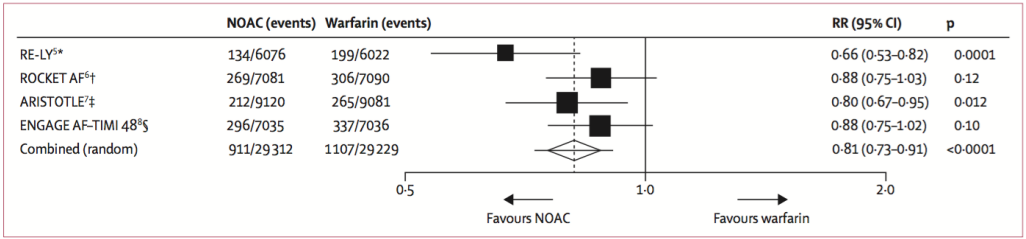


Figure 1: **Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Meta-analysis Secondary Efficacy and Safety, NOACs vs VKA

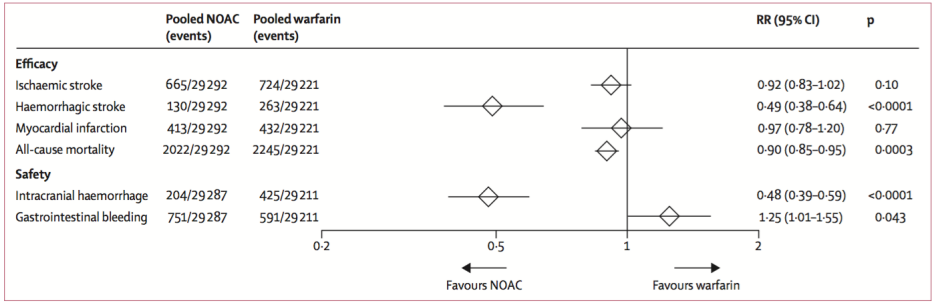


***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

Meta-analysis Major Bleeding, NOACs vs VKA

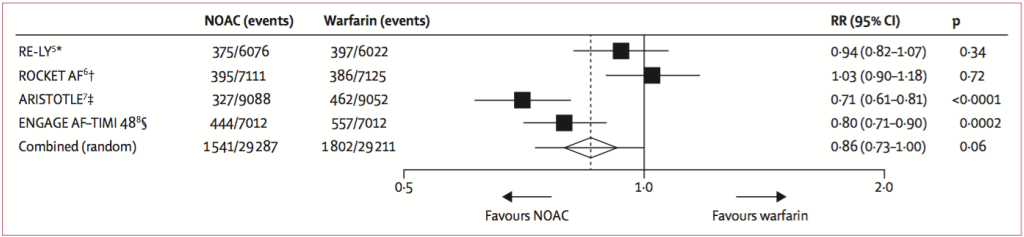


***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

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Glossary

- SPAF — Stroke prevention in AF
- RCT — Randomised controlled trial
- APTT — activated partial thromboplastin time
- tPA — tissue plasminogen activator