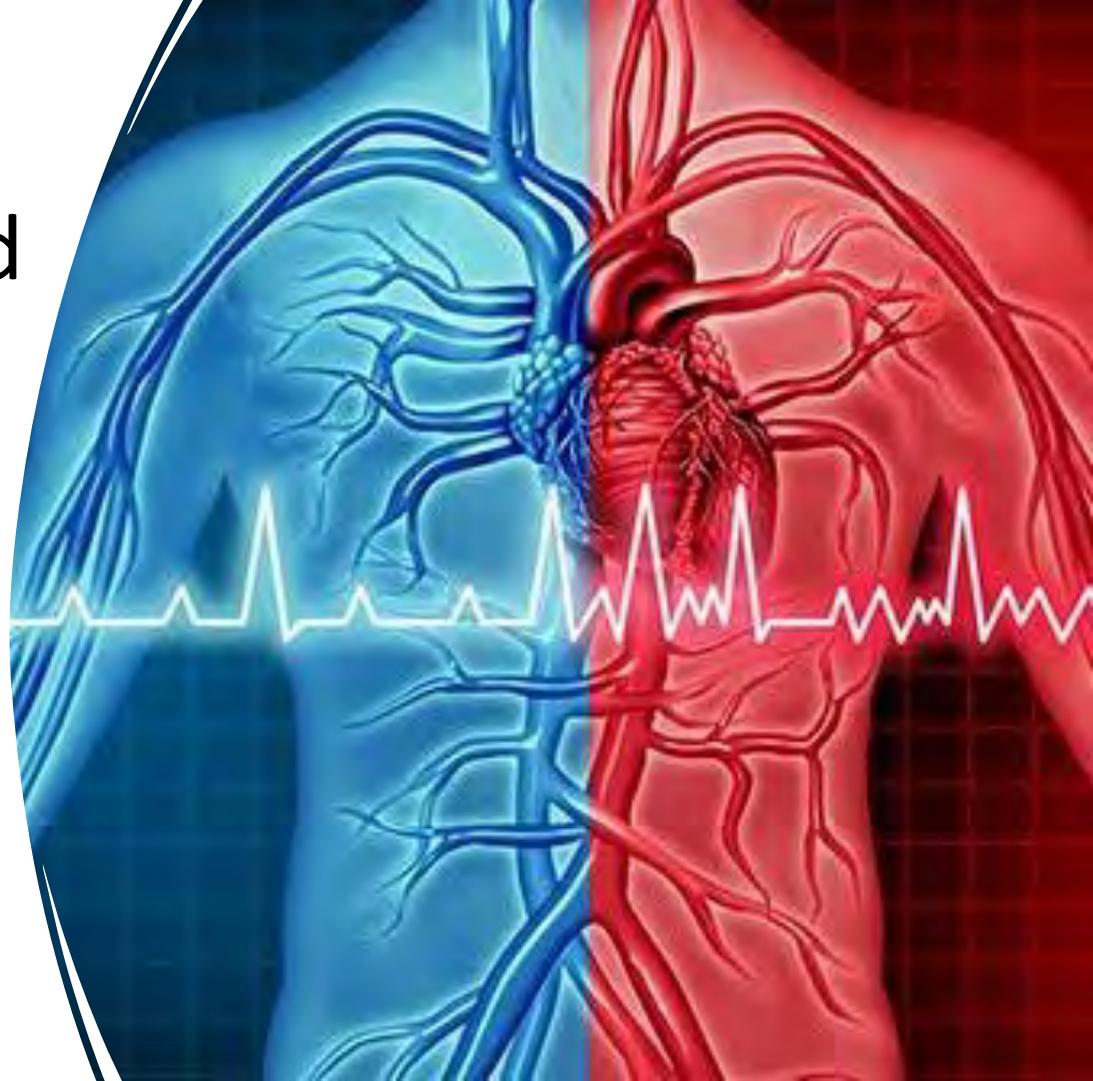
Atrial fibrillation and anticoagulation

Paul Wright MRPharmS (consultant) MSc IPresc

Consultant Cardiac Pharmacist

Barts Health NHS Trust

Twitter: @pharmBHC



Contents

- Pathophysiology of AF
- Detection of AF
- Consequences of AF
- Anticoagulation

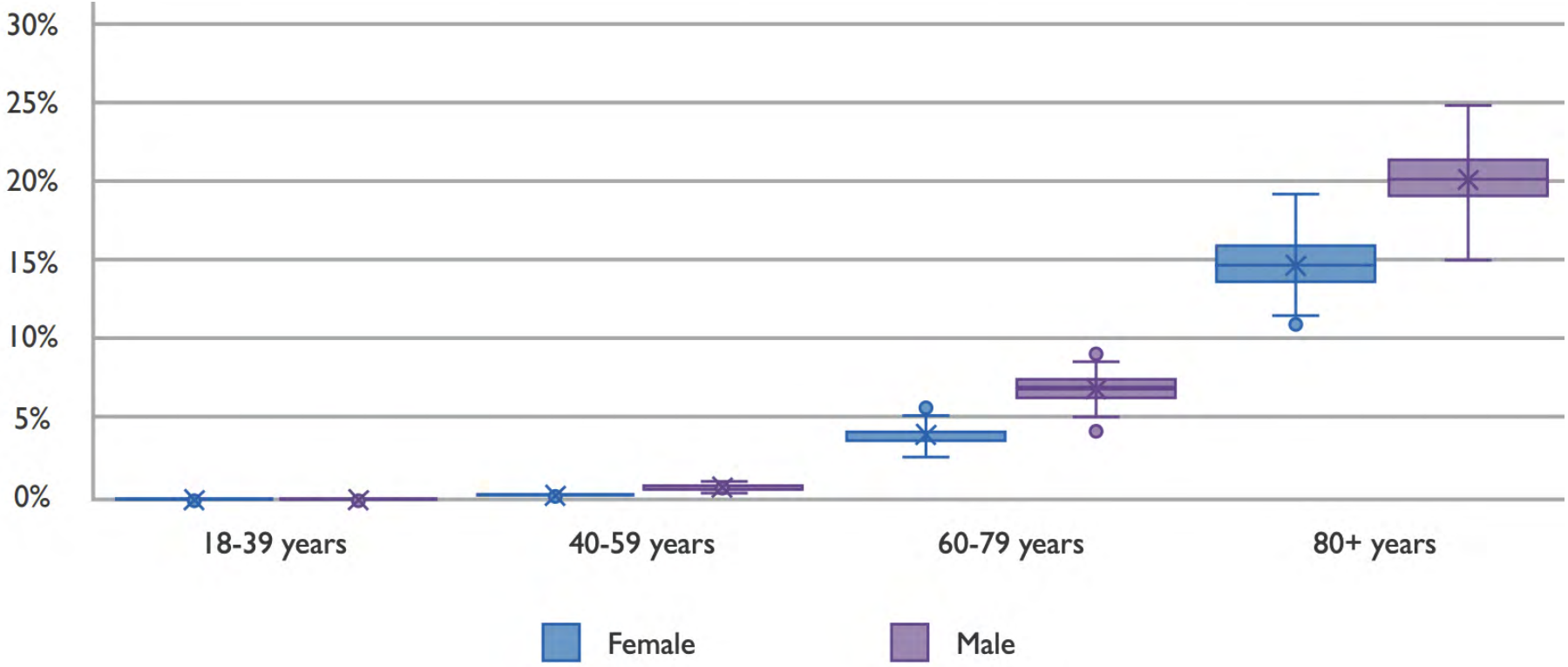
How common is atrial fibrillation?

The prevalence of GP recorded AF in England was 2.4%

- Prevalence of AF in males (2.8%) was higher than for females (2.0%)
- AF prevalence increased with age to 5.0% of those aged 60 to 79 years and 17.2% of those aged 80+
- AF prevalence recorded at CCG level ranged from 1.1% to 4.2%, with variation increasing with age

*Data from CVDPrevent

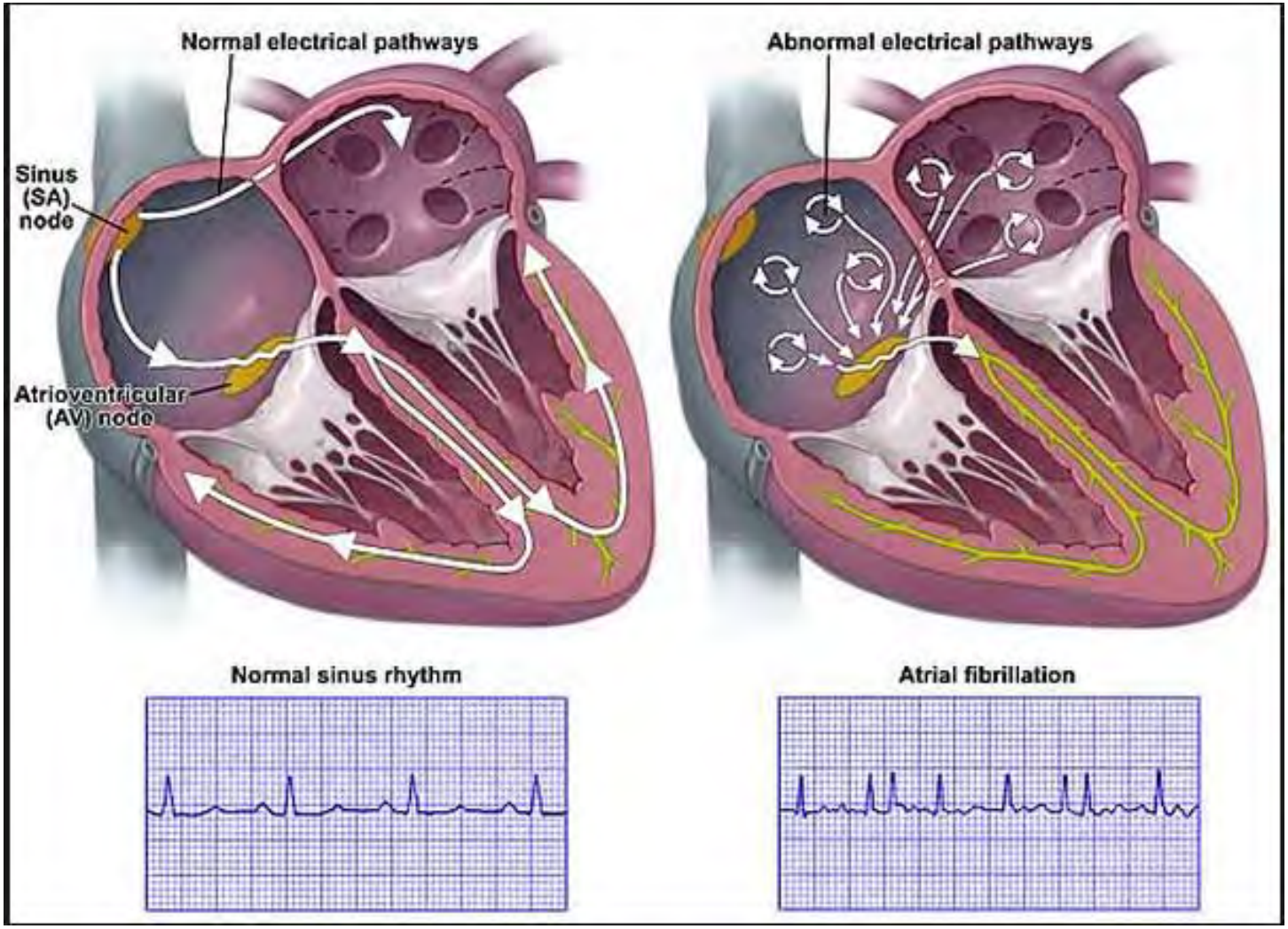
Prevalence of GP recorded AF in patients aged 18 and over, by age and sex



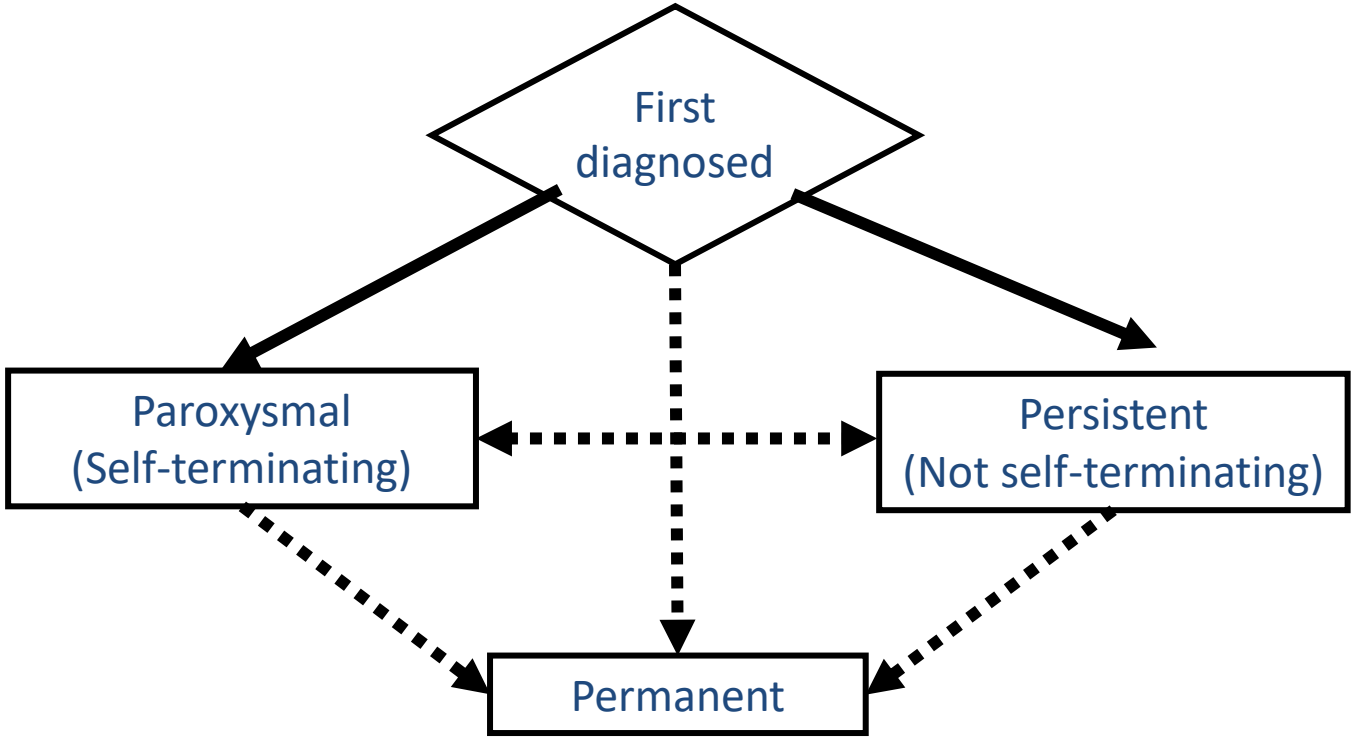
What is Atrial Fibrillation?

- AF is “A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction”. ESC 2021
- Electrocardiographic characteristics of AF include:
  - Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired),
  - Absence of distinct repeating P waves, and
  - Irregular atrial activations.

  OR simply - An irregularly irregular heart beat
- Most common sustained cardiac arrhythmia
- Irregular and **very rapid atrial rate** (>300-600 bpm)
- AV node cannot conduct all these impulses, however ventricular rate is still usually:
  - rapid (although not as rapid as atrial rate)
  - irregular


Normal electrical pathways
Abnormal electrical pathways
Sinus (SA) node
Atrioventricular (AV) node
Normal sinus rhythm
Atrial fibrillation

Classification of Atrial Fibrillation
ACC/AHA/ESC Guidelines



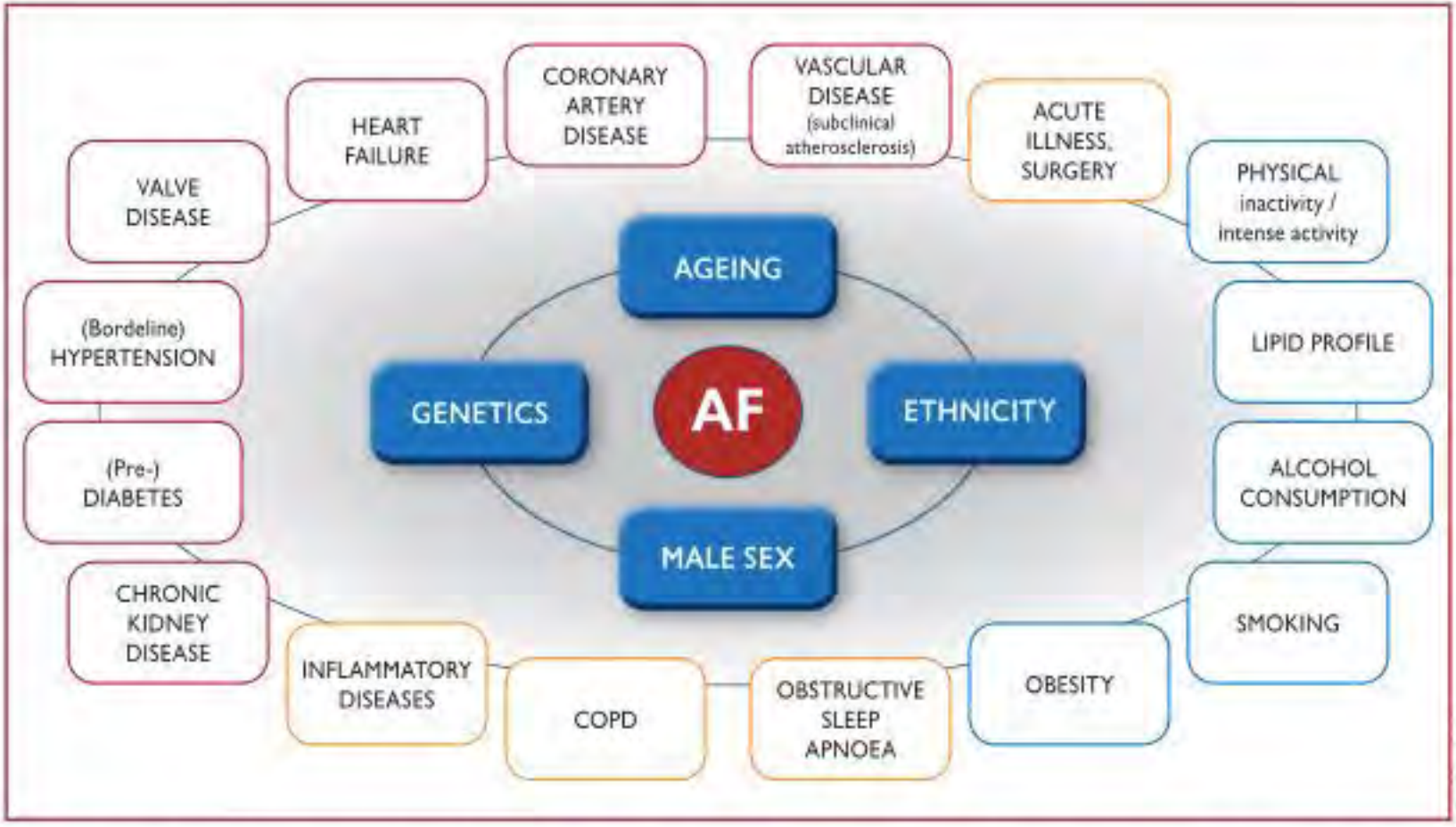


Figure 3 Summary of risk factors for incident AF[10,22,33,35–72] (*Supplementary Table 1* for full list). AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease.

Consequences of AF

- Reduced atrial function (“atrial kick”) and chamber synchronisation, *3 major consequences*:
    - *Impaired cardiac function of the heart*
    - *Tachycardia*
    - *Thrombogenesis*

- Anatomical changes that may become permanent if AF persists

- Patients with AF have a five-fold mean increase in risk of stroke.

Asymptomatic or Silent (!)

Symptomatic

Palpitations, dyspnoea, fatigue,

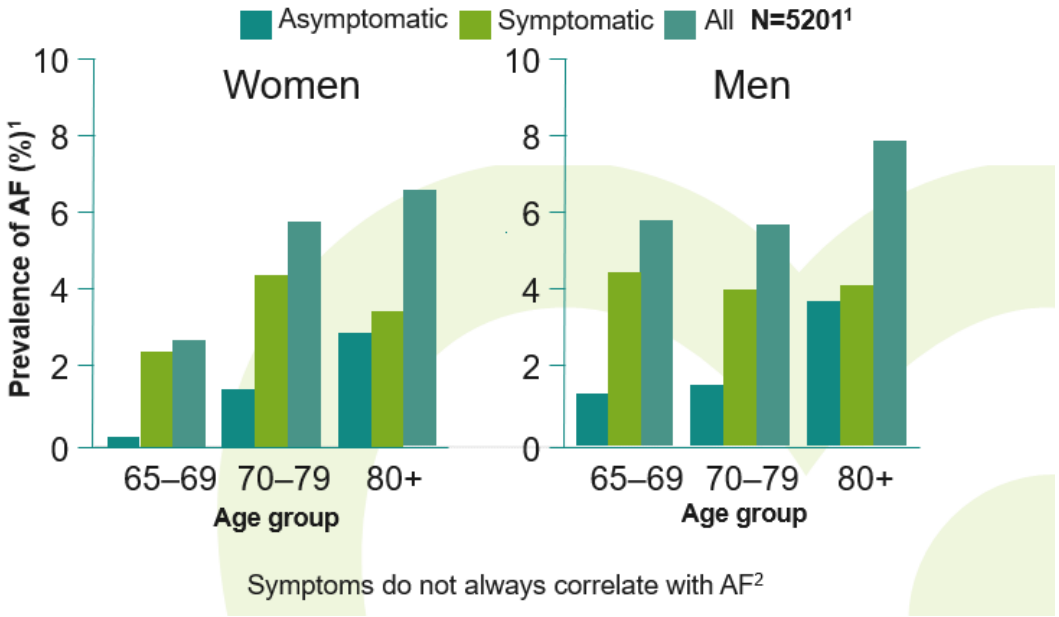
Chest tightness/pain, poor effort tolerance, dizziness, syncope, disordered sleep, etc.

Haemodynamically unstable

- Syncope
- Symptomatic hypotension
- Acute HF, pulmonary oedema
- Ongoing myocardial ischaemia
- Cardiogenic shock

Haemodynamically stable

A significant proportion of patients with AF are asymptomatic



Symptoms do not always correlate with AF[2]

1. Furberg C *et al, Am J Cardiol* 1994;74:236; 2. Savelieva I *et al, Pacing Clin Electrophysiol* 2000;23:145

Asymptomatic or Silent (!)

Symptomatic

Palpitations, dyspnoea, fatigue,

Chest tightness/pain, poor effort tolerance, dizziness, syncope, disordered sleep, etc.

Haemodynamically unstable

- Syncope
- Symptomatic hypotension
- Acute HF, pulmonary oedema
- Ongoing myocardial ischaemia
- Cardiogenic shock

Haemodynamically stable

AF-related OUTCOMES

AF-Related Outcome	Frequency in AF	Mechanism(s)
Death	1.5 - 3.5 fold increase	Excess mortality related to: • HF, comorbidities • Stroke
Stroke	20-30% of all ischaemic strokes, 10% of cryptogenic strokes	• Cardioembolic, or • Related to comorbid vascular atheroma
LV dysfunction / Heart failure	In 20-30% of AF patients	• Excessive ventricular rate • Irregular ventricular contractions • A primary underlying cause of AF
Cognitive decline / Vascular dementia	HR 1.4 / 1.6 (irrespective of stroke history)	• Brain white matter lesions, inflammation, • Hypoperfusion, • Micro-embolism

AF-related OUTCOMES

AF-Related Outcome	Frequency in AF	Mechanism(s)
Depression	Depression in 16-20% (even suicidal ideation)	• Severe symptoms and decreased QoL • Drug side effects
Impaired quality of life	>60% of patients	• Related to AF burden, comorbidities, psychological functioning and medication • Distressed personality type
Hospitalizations	10-40% annual hospitalization rate	• AF management, related to HF, MI or AF related symptoms • Treatment-associated complications

How to detect AF

Patient initiated (or medical professional) oscillometric blood pressure cuff

Pulse palpitation, auscultation

Patient initiated (or medical professional) intermittent ECG rhythm strip using smartphone or dedicated connectable device

Intermittent smartwatch ECG initiated by semi-continuous photoplethysmogram with prompt notification of irregular rhythm or symptoms

Wearable belts for continuous recordings

Stroke unit/in hospital telemetry monitoring

Patient initiated photoplethysmogram on smartphone

Semi-continuous photoplethysmogram on a smartwatch or wearable

Long-term Holter

1-2 week continuous ECG patches

Implantable cardiac monitors

KNOWYOUR ECG

Monitor your heart rhythm with a mobile ECG device

It records your heart rhythm and confirms if normal, AF suspected or if you should discuss the results with your doctor

For more information contact:
info@heartrhythmalliance.org

MyDiagnostick

- Hold the handles for 1 min
- Green or red light indicating absence or presence of AF
- No requirement to link with other devices

The Atrial Fibrillation challenge

1.4 million people have AF

1 in 4 people with AF are undiagnosed

66%

AF related strokes can be averted with treatment

Financial impact of AF

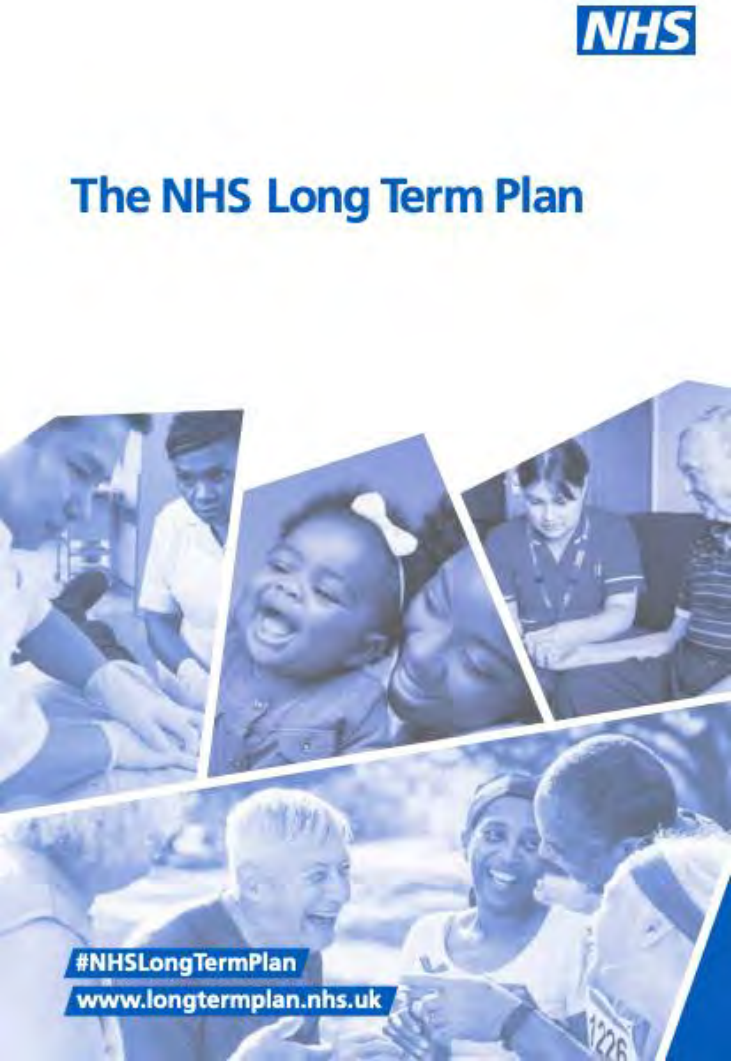
£2.2 Billion Healthcare costs

Atrial fibrillation and stroke

- 20% of all strokes linked to atrial fibrillation
- 62% were not prescribed oral anticoagulant
- People with AF **x5 higher risk** of stroke
- AF-related stroke cases more likely to die or be severely disabled

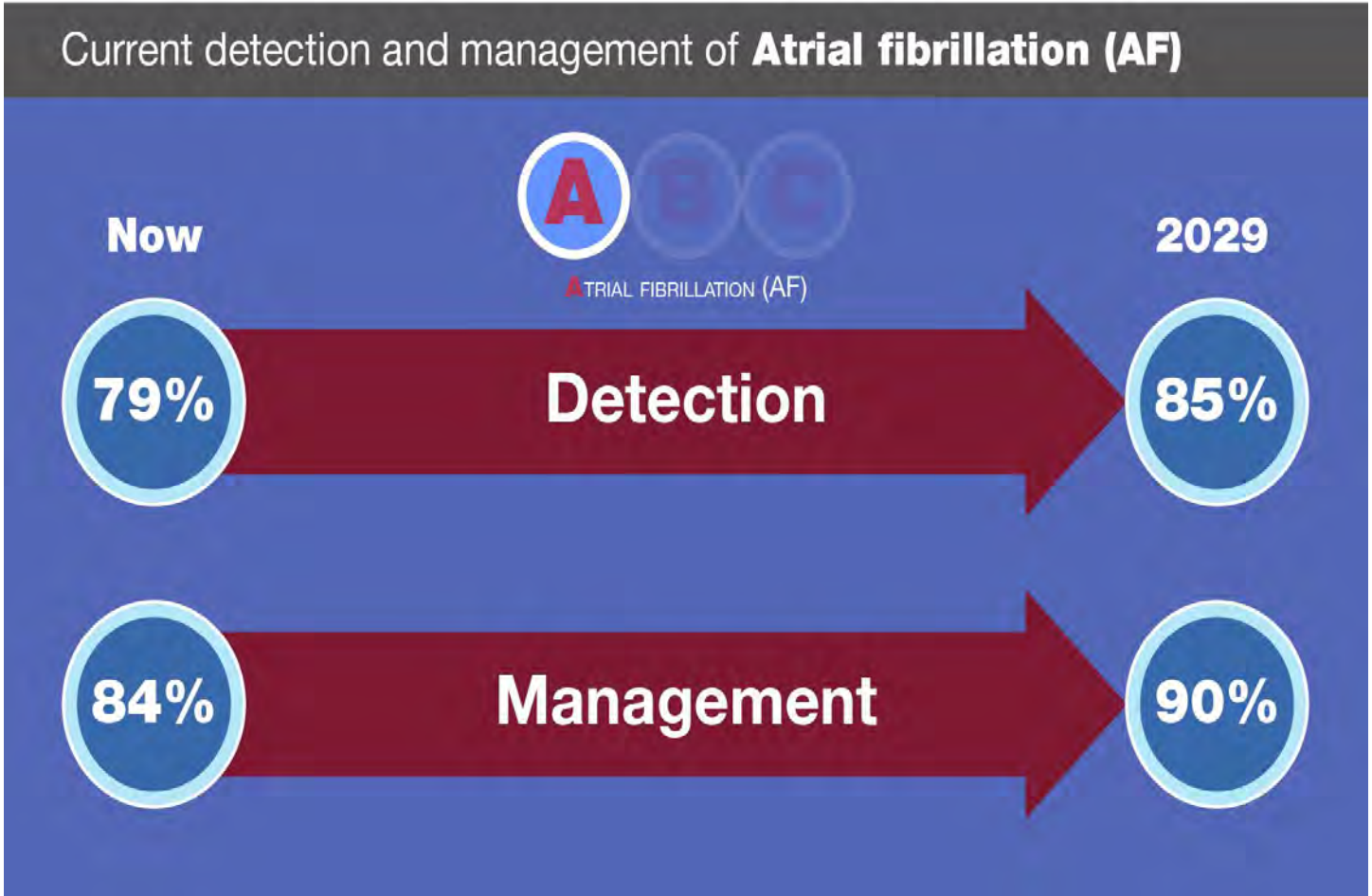
Ambition for prevention

Prevent 5000
AF strokes
over 5 years

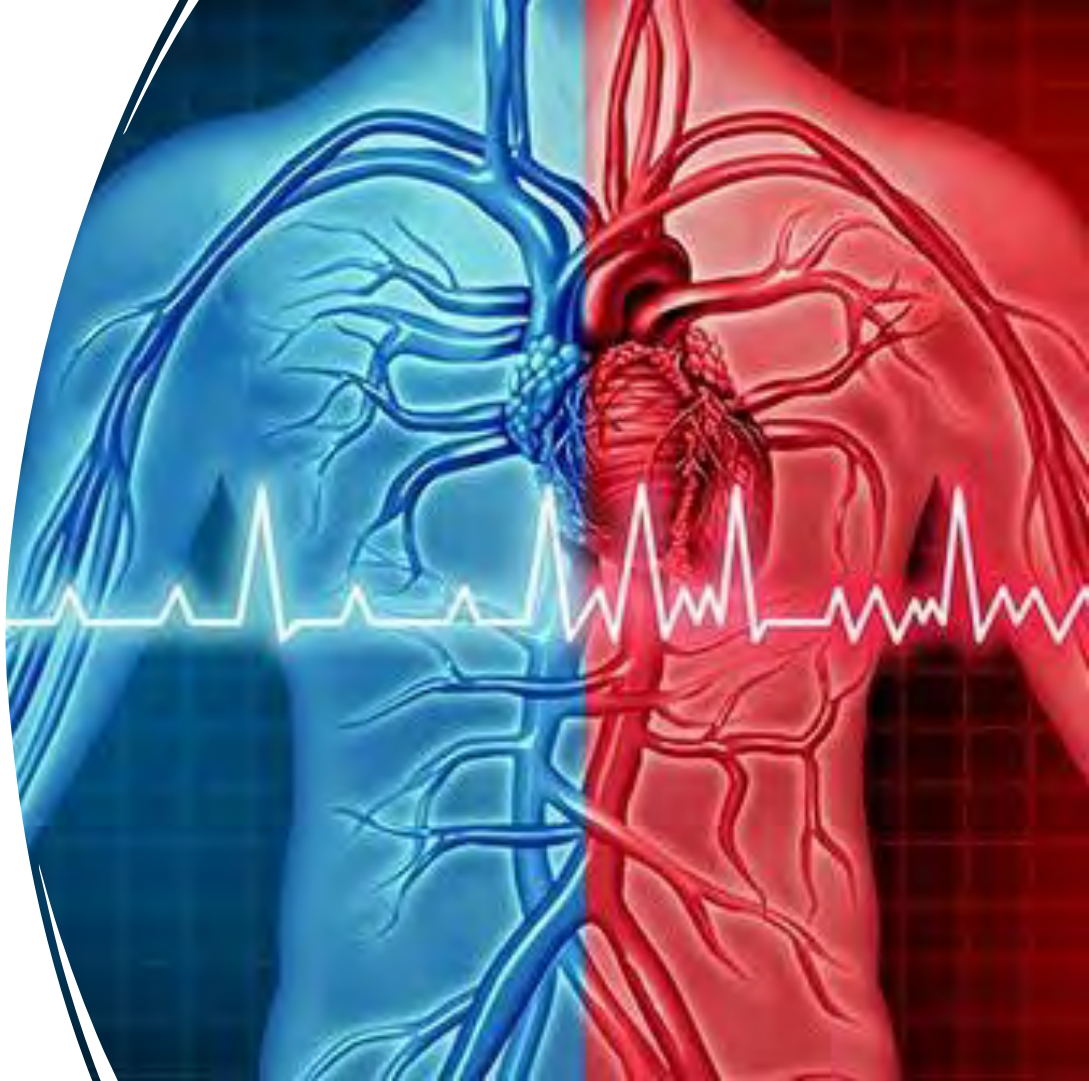


Detection and Protection ……

- **Early detection and treatment of CVD can help patients live longer, healthier lives.** Too many people are still living with undetected, high-risk conditions such as high blood pressure, raised cholesterol, and atrial fibrillation (AF)
- **Where individuals are identified with high risk conditions, appropriate preventative treatments will be offered in a timely way.** We will support pharmacists and nurses in primary care networks (see Chapter One) to case find and treat people with high-risk conditions. Where 100 people with AF are identified and receive anticoagulation medication, an average of four strokes are averted, preventing serious disability or even death


Current detection and management of **Atrial fibrillation (AF)**
A B C
ATRIAL FIBRILLATION (AF)
Now
2029
79%
Detection
85%
84%
Management
90%

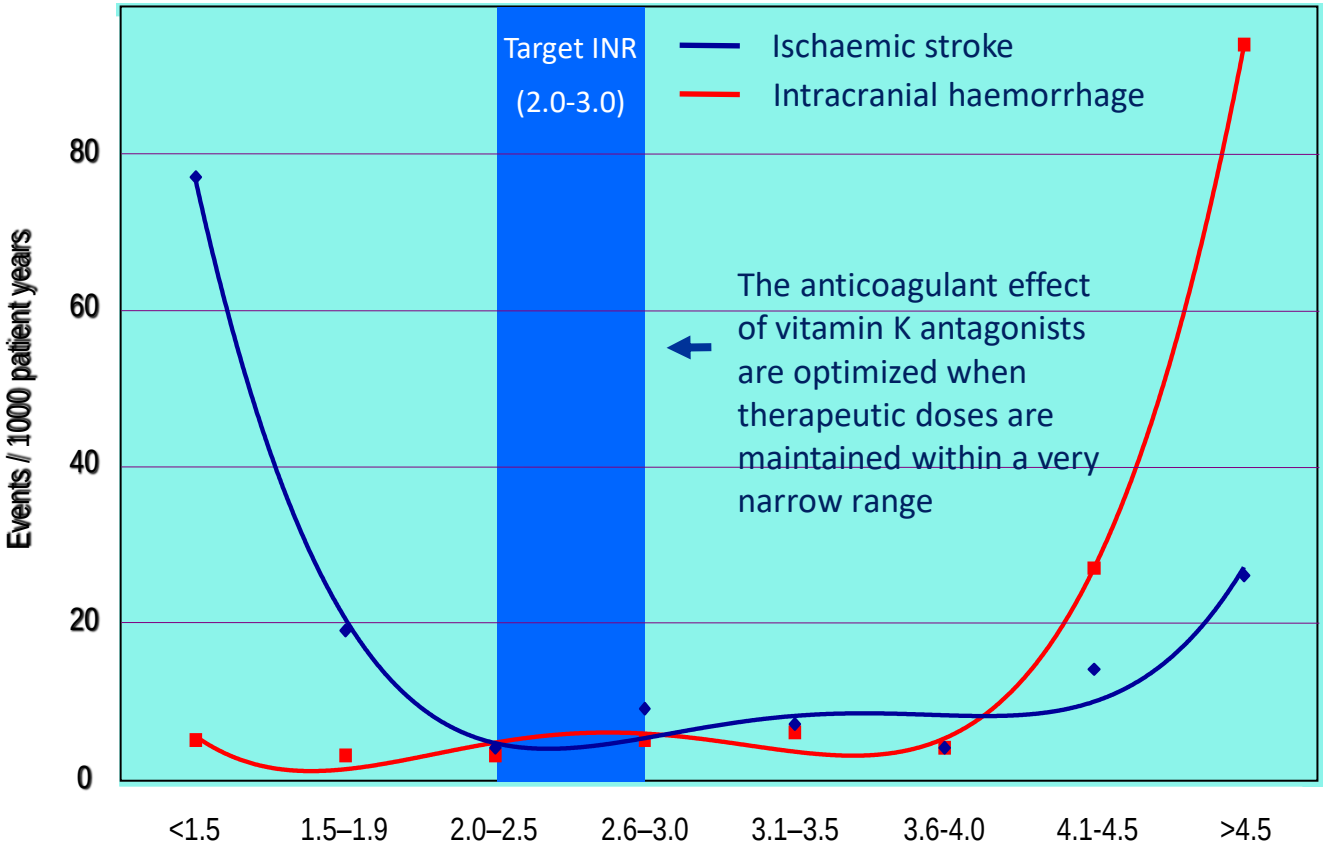
Anticoagulation



Warfarin

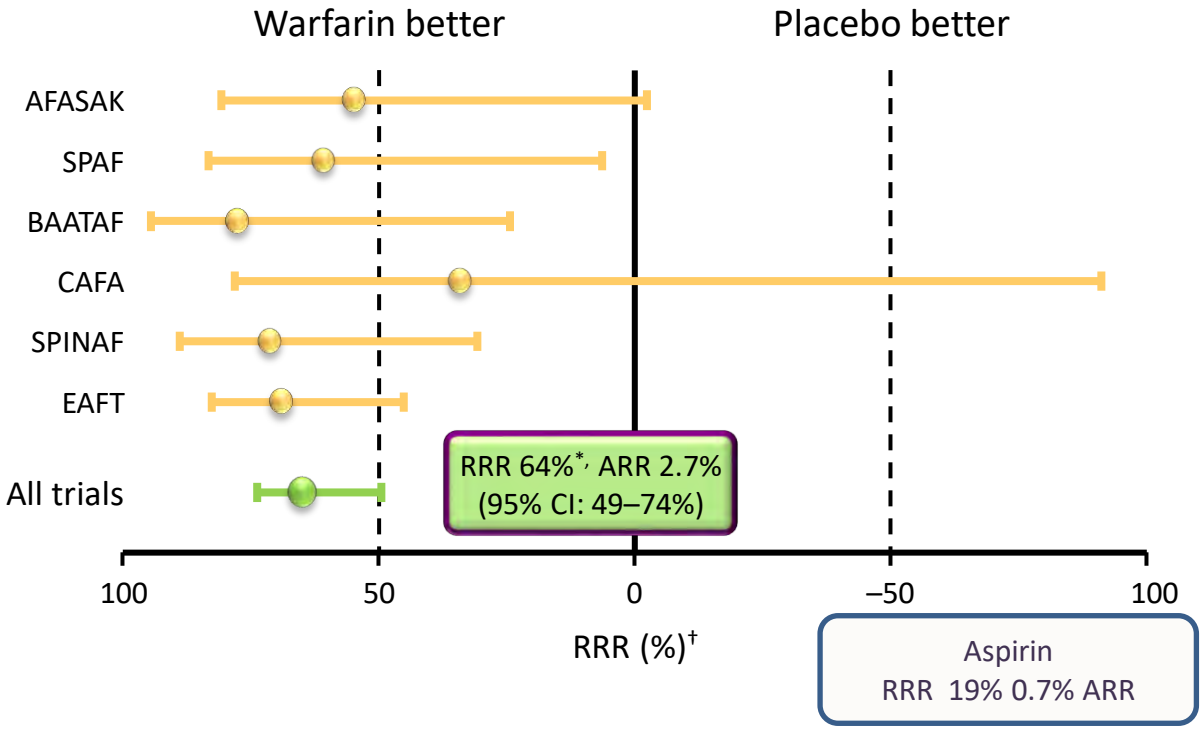
- Most commonly used anticoagulant worldwide
- Highly effective oral anticoagulant
- But it has its limitations….

Narrow therapeutic range with VKA



Hylek EM, et al. *N Eng J Med* 2003; 349:1019-1026.

Warfarin for non-rheumatic AF



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

*Random effects model; Error bars = 95% CI; *p>0.2 for homogeneity;*
†Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

Bleeding assessment

Risk tools validated in AF

HAS-BLED[33]	
Hypertension – uncontrolled (>160 mmHg systolic)	1
Abnormal renal function (SCr ≥200 μmol/L or dialysis or transplantation) or abnormal hepatic function[b]	1 or 2
Stroke history	1
Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis)	1
Labile INRs	1
Elderly (>65 years old)	1
Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week)	1 or 2
Maximum score	9

Potentially modifiable risk factors

Risk factors that may mandate a dose reduction of NOAC

Ref: *International Journal of General Medicine* 2016: **9;** 337–347

Risk tools validated in AF

HAS-BLED[33]		ATRIA[34]	
Hypertension – uncontrolled (>160 mmHg systolic)	1	Anemia[a]	3
Abnormal renal function (SCr ≥200 μmol/L or dialysis or transplantation) or abnormal hepatic function[b]	1 or 2	Severe renal disease (eGFR <30 mL/min or dialysis)	3
Stroke history	1	≥75 years old	2
Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis)	1	Any prior hemorrhage	1
Labile INRs	1	Diagnosed hypertension	1
Elderly (>65 years old)	1	–	–
Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week)	1 or 2	–	–
Maximum score	9	Maximum score	10

Potentially modifiable risk factors

Risk factors that may mandate a dose reduction of NOAC

Ref: *International Journal of General Medicine* 2016: **9;** 337–347

Risk tools validated in AF

HAS-BLED[33]		ATRIA[34]		ORBIT[35]	
Hypertension – uncontrolled (>160 mmHg systolic)	1	Anemia[a]	3	Older age (≥75 years old)	1
Abnormal renal function (SCr ≥200 µmol/L or dialysis or transplantation) or abnormal hepatic function[b]	1 or 2	Severe renal disease (eGFR <30 mL/min or dialysis)	3	Reduced hemoglobin[a], reduced hematocrit[c], or anemia	2
Stroke history	1	≥75 years old	2	Bleeding history	2
Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis)	1	Any prior hemorrhage	1	Insufficient kidney function (eGFR <60 mg/dL/1.73 m²)	1
Labile INRs	1	Diagnosed hypertension	1	Treatment with antiplatelets	1
Elderly (>65 years old)	1	–	–	–	–
Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week)	1 or 2	–	–	–	–
Maximum score	9	Maximum score	10	Maximum score	7

Potentially modifiable risk factors

Risk factors that may mandate a dose reduction of NOAC

Ref: *International Journal of General Medicine* 2016: **9;** 337–347

Assessment of Risk of Bleeding - ORBIT

- Major bleeding - defined as fatal bleeding, symptomatic bleeding in a critical organ, or bleeding with a hemoglobin drop requiring transfusion of ≥2 units (ISTH criteria).
- ORBIT does not take into account choice of anticoagulant.
- Unlike HAS-BLED, ORBIT does not take into account the time in therapeutic range, as there is no reliable or readily available objective measure for therapeutic range of the direct oral anticoagulants (DOACs).
- Unlike HAS-BLED, ORBIT was derived in a patient population that included vitamin K antagonists (VKAs, such as warfarin) as well as DOACs.

ORBIT Bleeding Risk Score for Atrial Fibrillation ☆

Predicts bleeding risk in patients on anticoagulation for afib, similar to HAS-BLED.

Sex	Male	
Hemoglobin <12 g/dL or h…		
Treatment with antiplatelet agents	No 0	Yes +1

ORBIT Score	Risk group	Bleeds per 100 patient-years
0-2	Low	2.4
3	Medium	4.7
4-7	High	8.1

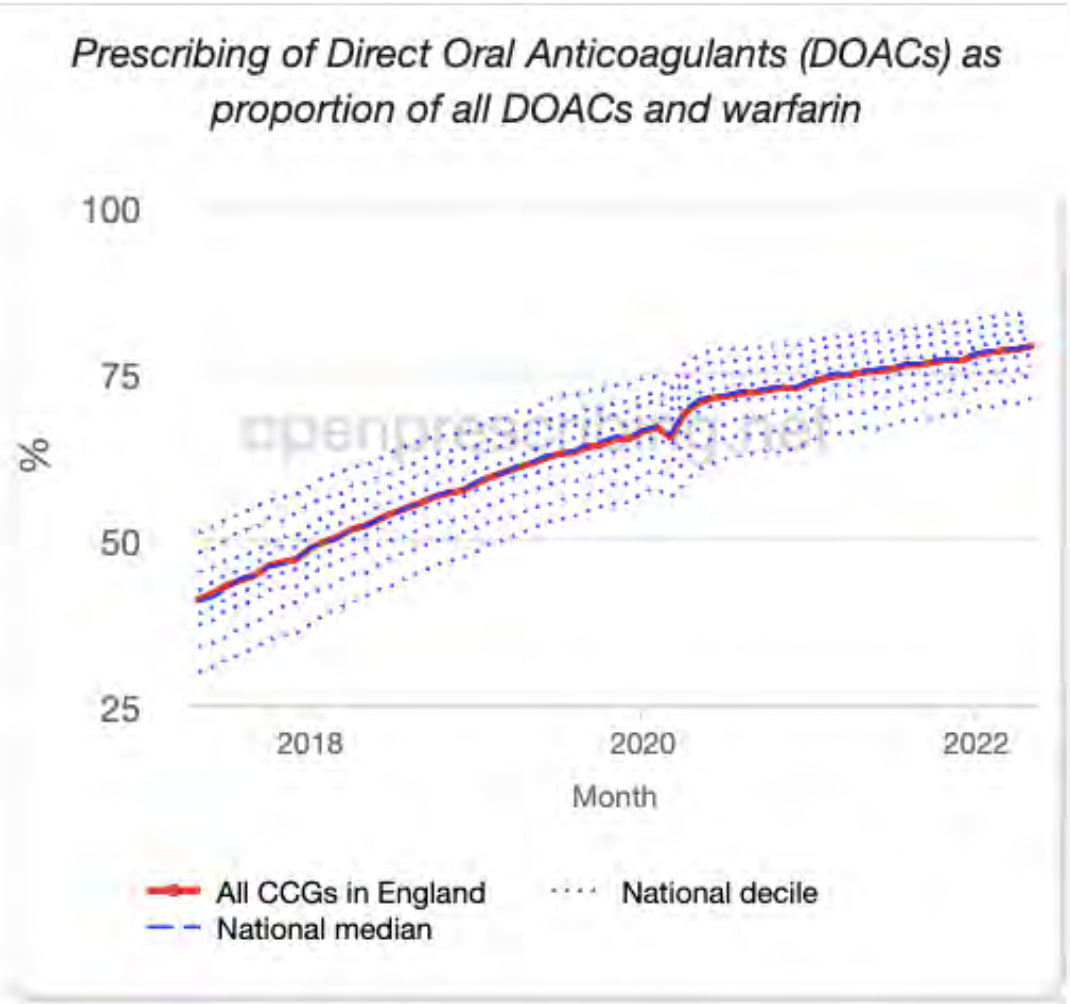
Signs and Symptoms of Bleeding

- Epistaxis, gum bleeding, bleeding from cuts or scrapes or heavier than usual menstrual period
- Severe worsening bruising not due to injury
- Red or dark urine
- Red or black bowel motions
- Coughing blood
- Dark or blood stained vomit
- Severe headache or dizziness

Reducing Risk of Bleeding

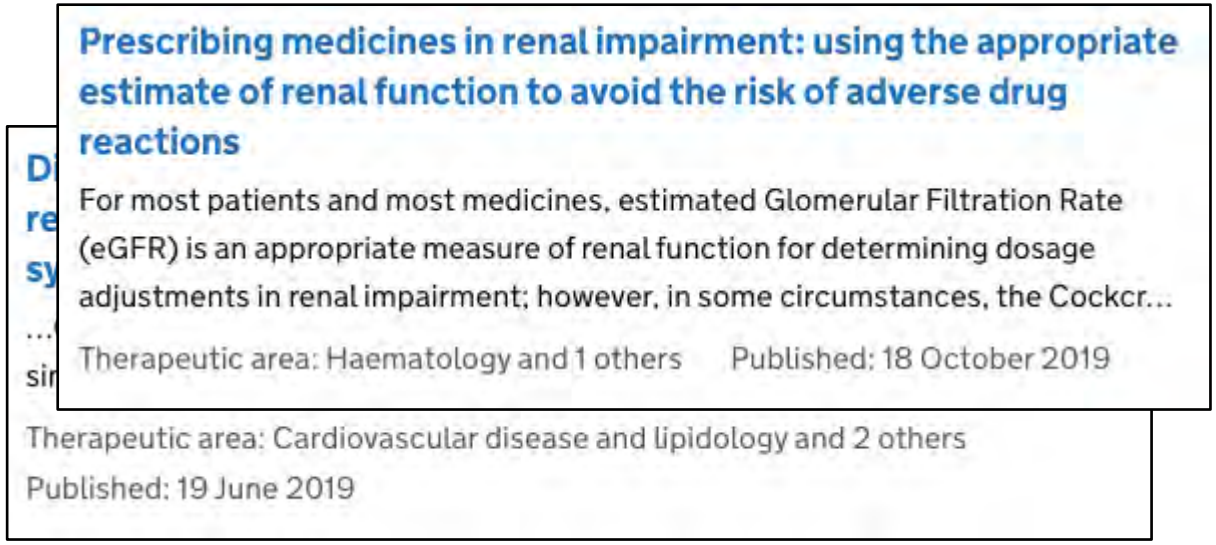
- Address uncontrolled hypertension
- Review benefit/risk of concomitant aspirin:
  - Hypertensives, diabetics, CHD and no acute ischemic event or intervention in the last year
  - Stop aspirin when INR in therapeutic range
- Risk of bleeding is greatest in first 90 days of OAC therapy
  - Caution : drug interactions and new drugs
  - Close or more frequent monitoring
- Review concomitant use of NSAIDS
- Consider a PPI

Hylek, E.M., Evans-Molina, C, Shea, C. et al. (2007), Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation, Circulation, 115, 2689-2696.



www.openprescribing.net

MHRA alerts


Prescribing medicines in renal impairment: using the appropriate estimate of renal function to avoid the risk of adverse drug reactions
For most patients and most medicines, estimated Glomerular Filtration Rate (eGFR) is an appropriate measure of renal function for determining dosage adjustments in renal impairment; however, in some circumstances, the Cockcr...
Therapeutic area: Haematology and 1 others
Published: 18 October 2019
Therapeutic area: Cardiovascular disease and lipidology and 2 others
Published: 19 June 2019

Open access Original research

BMJ Open

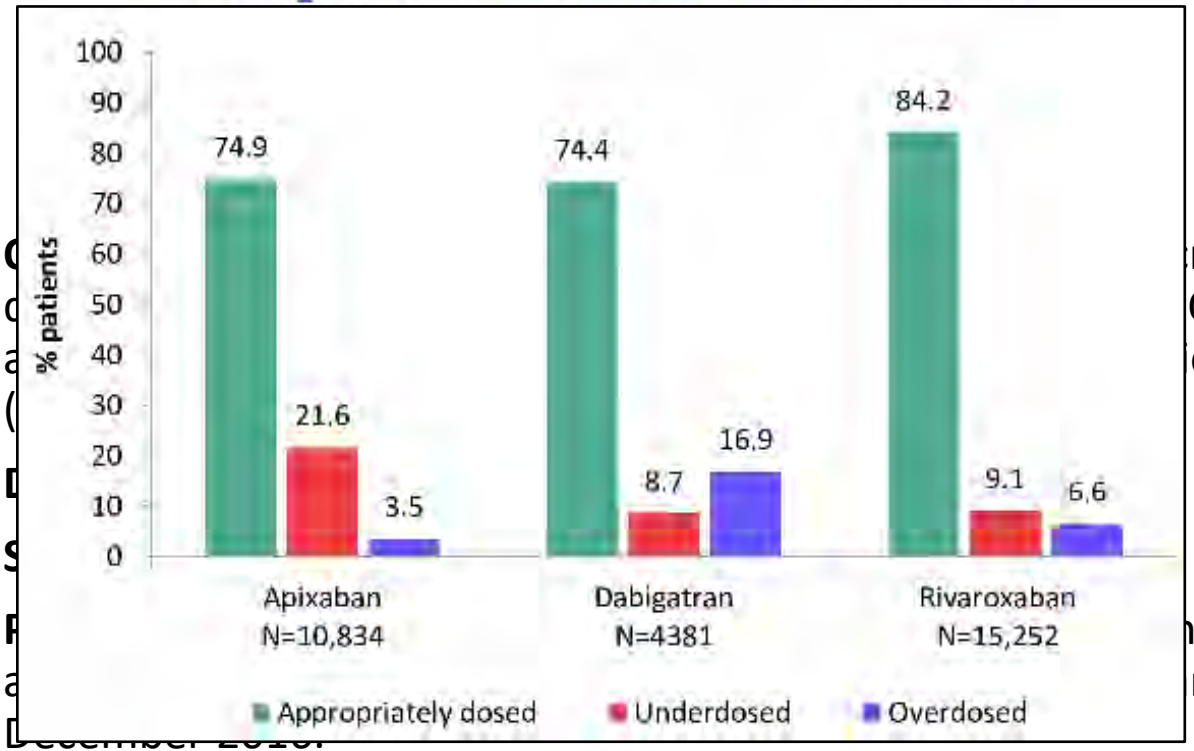
Appropriateness of initial dose of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation in the UK

Luis Alberto García Rodríguez,[1] Mar Martín-Pérez,[1] Pareen Vora,[2] Luke Roberts,[3] Yanina Balabanova,[2] Gunnar Brobert,[4] Samuel Fatoba,[5] Kiliana Suzart-Woischnik,[2] Bernhard Schaefer,[2] Ana Ruigomez[1]

- **Objective** To evaluate the appropriateness of the initial prescribed daily dose of non-vitamin K antagonist oral anticoagulants (NOACs) according to label in patients with non-valvular atrial fibrillation (NVAF) in the UK.
- **Design** Population-based cross-sectional study.
- **Setting** UK primary care.
- **Population** 30 467 patients with NVAF and a first prescription for apixaban, dabigatran or rivaroxaban between January 2011 and December 2016.

BMJ Open

Appropriateness of initial dose of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial



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  December 2016.

How to assess renal function?

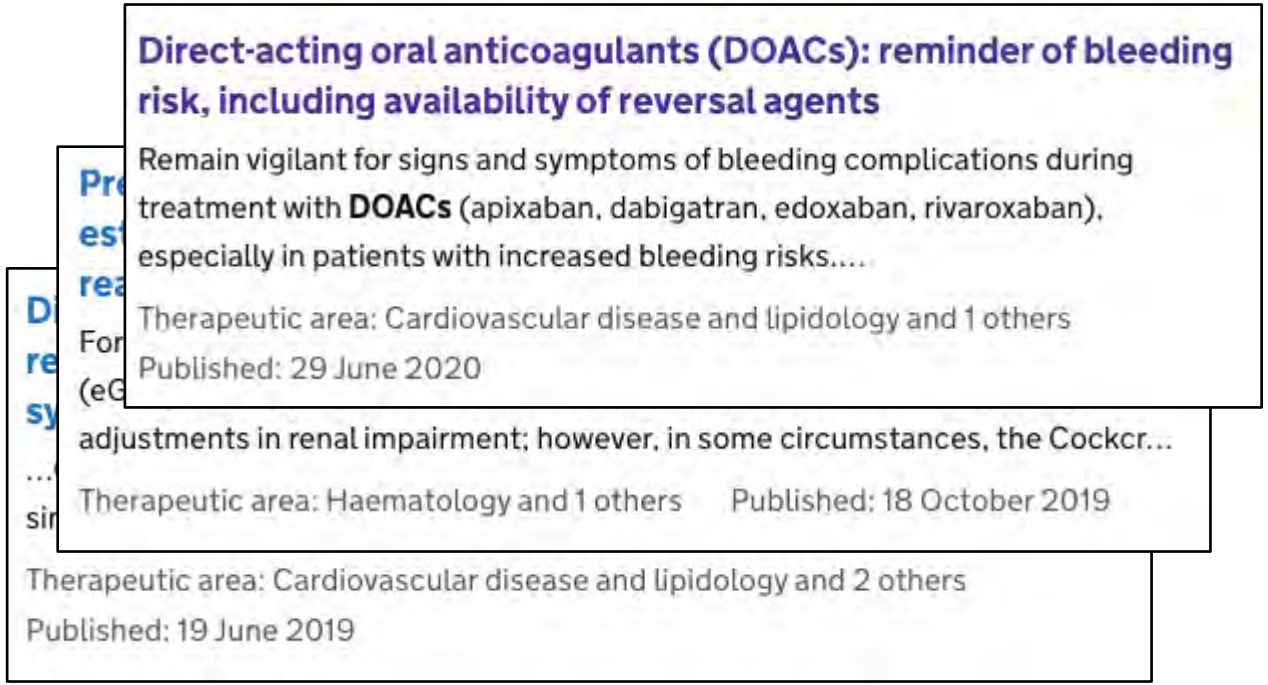
- NOAC trials used CrCl to estimate renal function, hence SPCs recommend this method
- eGFR may overestimate for ages > 65yrs, CrCl may underestimate for ages >65yrs[1]
- Extremes of body weight can over/under estimate renal function

Cockcroft–Gault: $$CrCl = \frac{\{(140 - age) * (weight\ in\ kg) * (F)\}}{Serum\ creatinine}$$

Where F = 1.23 if male or 1.04 if female

[1] MacCallum PK et al. BMJ Open 2013;3:e003343.

MHRA alerts


Direct-acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents
Remain vigilant for signs and symptoms of bleeding complications during treatment with DOACs (apixaban, dabigatran, edoxaban, rivaroxaban), especially in patients with increased bleeding risks....
Therapeutic area: Cardiovascular disease and lipidology and 1 others
Published: 29 June 2020
adjustments in renal impairment; however, in some circumstances, the Cockcr...
Therapeutic area: Haematology and 1 others
Published: 18 October 2019
Therapeutic area: Cardiovascular disease and lipidology and 2 others
Published: 19 June 2019

Reversal of the anticoagulant effect of dabigatran: idarucizumab

Evidence summary [ESNM73] Published: 24 May 2016

Summary

Idarucizumab is the first agent to be licensed in the UK that reverses the anticoagulant effect of a non-vitamin K antagonist oral anticoagulant (NOAC). Its action is specific against the NOAC dabigatran etexilate. In the interim analysis of an ongoing, phase III, uncontrolled, cohort study (RE-VERSE AD; n=90), treatment with a 5 g dose of idarucizumab completely reversed the anticoagulant effect of dabigatran etexilate in adults who had either serious bleeding or required urgent surgery. People may still need other supportive measures, for example blood products, to manage their bleeding and these should be considered as medically appropriate.

Regulatory status: Idarucizumab (Praxbind, Boehringer Ingelheim Limited) was launched in the UK in December 2015. It is licensed for use i Summary :reated with dabigatran etexilate (Pradaxa, Boehringer Ingelheim Limited) when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.

Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban

Technology appraisal guidance [TA697] Published: 12 May 2021

1 Recommendations

1.1 Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract, and
- the company provides andexanet alfa according to the commercial arrangement.

1.2 Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.

MHRA alerts

Warfarin and other anticoagulants: monitoring of patients during the COVID-19 pandemic

Guidance has been published on monitoring of patients on warfarin and other anticoagulants during the COVID-19 pandemic.

Therapeutic area: Haematology Published: 22 October 2020

National Patient Safety Alert

NHS

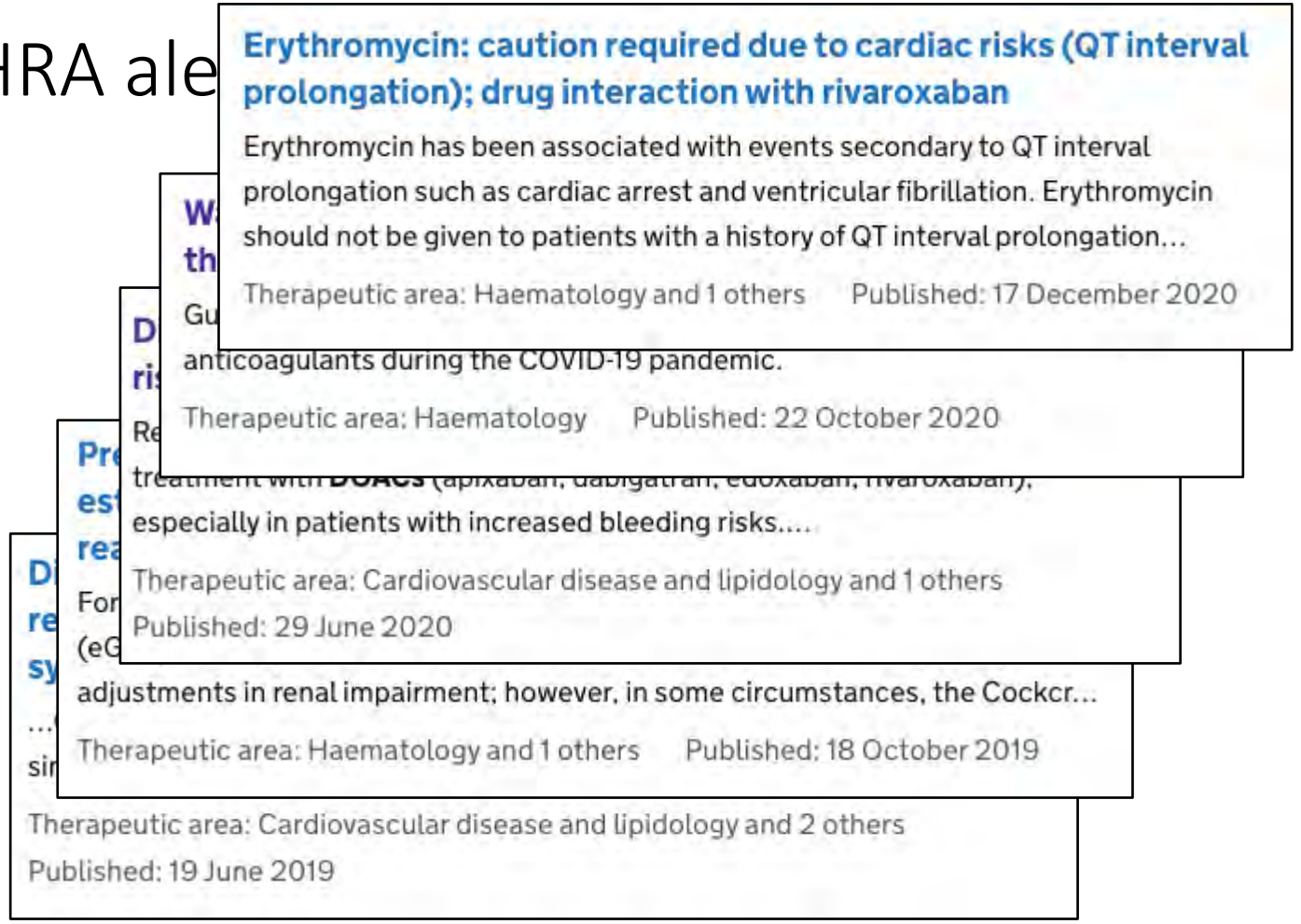
Inappropriate anticoagulation of patients with a mechanical heart valve

Date of Issue:	14 July 2021	Reference no:	NatPSA/2021/006/NHSPS

This alert is for action by: general practices, NHS-funded services providing anticoagulation review services (eg in community pharmacy, general practices and hospitals), and mental health and learning disability trusts providing general practice care (eg within forensic services).

This is a safety critical and complex National Patient Safety Alert. Implementation should be co-ordinated by an executive lead (or equivalent role in organisations without executive boards) and supported by clinical leaders in anticoagulation services and cardiology.

MHRA ale


Erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban
Erythromycin has been associated with events secondary to QT interval prolongation such as cardiac arrest and ventricular fibrillation. Erythromycin should not be given to patients with a history of QT interval prolongation…
Therapeutic area: Haematology and 1 others
Published: 17 December 2020
anticoagulants during the COVID-19 pandemic.
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Published: 22 October 2020
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Therapeutic area: Cardiovascular disease and lipidology and 1 others
Published: 29 June 2020
adjustments in renal impairment; however, in some circumstances, the Cockcr...
Therapeutic area: Haematology and 1 others
Published: 18 October 2019
Therapeutic area: Cardiovascular disease and lipidology and 2 others
Published: 19 June 2019

Stroke prevention

CHA_2DS_2-VASc ≥ 2
offer oral anticoagulant

CHA_2DS_2-VASc = 1 in men
consider oral anticoagulant

CHA_2DS_2-VASc ≤ 1 in women or
CHA_2DS_2-VASc = 0 in men
do not offer an anticoagulant

Review at age 65 or if the person develops diabetes or cardiovascular comorbidities

Discuss risks and benefits of anticoagulation, including that for most people the benefit of anticoagulation outweighs the bleeding risk.

Direct-acting anticoagulants (DOACs)

- Offer a DOAC as first-choice anticoagulant
- Discuss choice of DOAC, taking into account clinical features, contraindications and the person's preference. Follow guidance in the BNF and the MHRA advice on direct-acting oral anticoagulants
- For people already stable on a vitamin K antagonist, discuss switching at their next routine appointment, taking into account time in therapeutic range (TTR)

Vitamin K antagonists

- Use a vitamin K antagonist if DOACs are contraindicated or not tolerated
- Calculate the person's TTR at each visit. Reassess anticoagulation if poorly controlled (2 INR values >5 or 1 INR value >8 or 2 INR values <1.5 in past 6 months or TTR <65%)
- Take into account and address factors that may contribute to poor control
- Discuss the risks and benefits of alternative stroke prevention strategies with the person

Left atrial appendage occlusion

- If anticoagulation is contraindicated or not tolerated consider left atrial appendage occlusion

Table 1. Comparison of Warfarin and DOACs

	Warfarin[8]	Dabigatran[7]	Rivaroxaban[3,9]	Apixaban[4,10]	Edoxaban[6,11]
Target	Vitamin K epoxide reductase	Free and clot-bound thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Bioavailability	>95%	6.5%	>80%	50%	62%
Metabolism	Hepatic; primarily metabolized by CYP2C9; also metabolized by CYP1A2 and CYP3A4	Renal; 80% renally excreted unchanged; not a substrate of CYP450 enzymes; substrate of P-gp	1/3 excreted renally unchanged; 2/3 metabolized by CYP3A4 and CYP2J2; substrate of P-gp	Hepatic; 73% metabolized to inactive metabolites, mainly by CYP3A4; substrate of P-gp	Stays largely unchanged; minimally metabolized by hepatic CYP450 pathway; substrate of P-gp
Plasma protein binding	97%	34%-35%	~92%-95%	87%	55%
Half-life (h)	40	14-17	5-9	10-14	10-14
Elimination	92% renal	80% renal, 20% fecal	66% renal, 33% fecal	27% renal, 63% fecal	50% renal, 50% biliary and fecal
Peak effect (h)	72-96	2	2-4	3-4	1-2

Abbreviations: CYP1A2, cytochrome P-450 1A2; CYP2C9, cytochrome P-450 2C9; CYP2J2, cytochrome P-450 2J2; CYP3A4, cytochrome P-450 3A4; CYP450, cytochrome P-450; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein 1.

Ref: https://www.consultant360.com/articles/direct-oral-anticoagulants-user-s-guide

Table 3. Major Studies on the Use of DOACs in Nonvalvular AF

	RE-LY[6] (N=18,113)	ROCKET AF[12] (N=14,264)	ARISTOTLE[13] (N=18,201)	ENGAGE AF-TIMI 48[14] (N=21,105)
Drug regimen	Dabigatran 150 mg twice daily/75 mg twice daily reduced	Rivaroxaban 20 mg daily/15 mg daily reduced	Apixaban 5 mg twice daily/2.5 mg twice daily reduced	Edoxaban 60 mg daily/ 30 mg daily reduced
Trial design	Randomized open-label	Randomized double-blind	Randomized double-blind	Randomized double-blind
Mean age (y)	71.5	73	70	72
Mean $CHADS_2$ score	2.2±1.2 in dabigatran group vs 2.1±1.1 in warfarin group	3.48±0.94 in rivaroxaban group vs 3.46±0.95 in warfarin group	2.1±1.1 in apixaban and warfarin groups	2.8±1.0 in edoxaban and warfarin groups
% with prior CVA	20.3 vs 19.8	54.9 vs 54.6	19.2 vs 19.7	28.1 vs 28.3
TTR in warfarin arm	64%	55%	62.2%	64.9%
Stroke/systemic embolism (HR [95% CI])	0.66 (0.53-0.82)	0.88 (0.75-1.03)	0.79 (0.66-0.95)	0.68 (0.55-0.84)[a]
Ischemic stroke (HR [95% CI])	0.76 (0.60-0.98)	0.94 (0.75-1.17)	0.92 (0.74-1.13)	0.80 (0.62-1.04)[a]
Hemorrhagic stroke (HR [95% CI])	0.26 (0.14-0.49)	0.59 (0.37-0.93)	0.51 (0.35-0.75)	0.49 (0.32-0.74)[a]
All-cause mortality (HR [95% CI])	0.88 (0.77-1)	0.85 (0.70-1.02)	0.89 (0.80-0.99)	0.92 (0.83-1.01)
Major bleed (HR [95% CI])	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.84 (0.73-0.97)[a]
GI bleed (HR [95% CI])	1.50 (1.19-1.89)	1.39 (1.19-1.61)	0.89 (0.70-1.15)	1.40 (1.13-1.73)[a]
CV mortality (HR [95% CI])	0.86 (0.72-0.99)	0.89 (0.73-1.10)	0.89 (0.76-1.04)	0.82 (0.72-0.93)[a]

Legend: Red represents a statistically significant increase; green represents a statistically significant decrease.
Abbreviations: AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; CVA, cerebrovascular accident; DOAC, direct oral anticoagulant; GI, gastrointestinal; HR, hazard ratio; TTR, time in therapeutic range.
[a] HRs based on events for the edoxaban-indicated population (creatinine clearance ≤95 mL/min in the 60-mg edoxaban population).

EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1], M.D., Ph.D., Peter Verhamme[1], M.D., Ph.D., Marco Alings[2], M.D., Ph.D., Matthias Antz[3], M.D., Werner Hacke[4], M.D., Jonas Oldgren[5], M.D., Ph.D., Peter Sinnaeve[1], M.D., Ph.D., A. John Camm[6], M.D., Paulus Kirchhof[7], M.D., Ph.D.

1. Department of Cardiovascular Medicine, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium; 2. Department of Cardiology, Amphia Ziekenhuis, Breda, Netherlands; 3. Department of Cardiology, Klinikum Oldenburg, Oldenburg, Germany; 4. Department of Neurology, Ruprecht Karls Universität, Heidelberg, Germany; 5. Uppsala Clinical Research Center and Dept of Medical Sciences, Uppsala University, Uppsala, Sweden; 6. Clinical Cardiology, St George's University, London, United Kingdom; 7. University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK, and Department of Cardiology and Angiology, University of Münster, Germany

EUROPEAN Heart Rhythm ASSOCIATION
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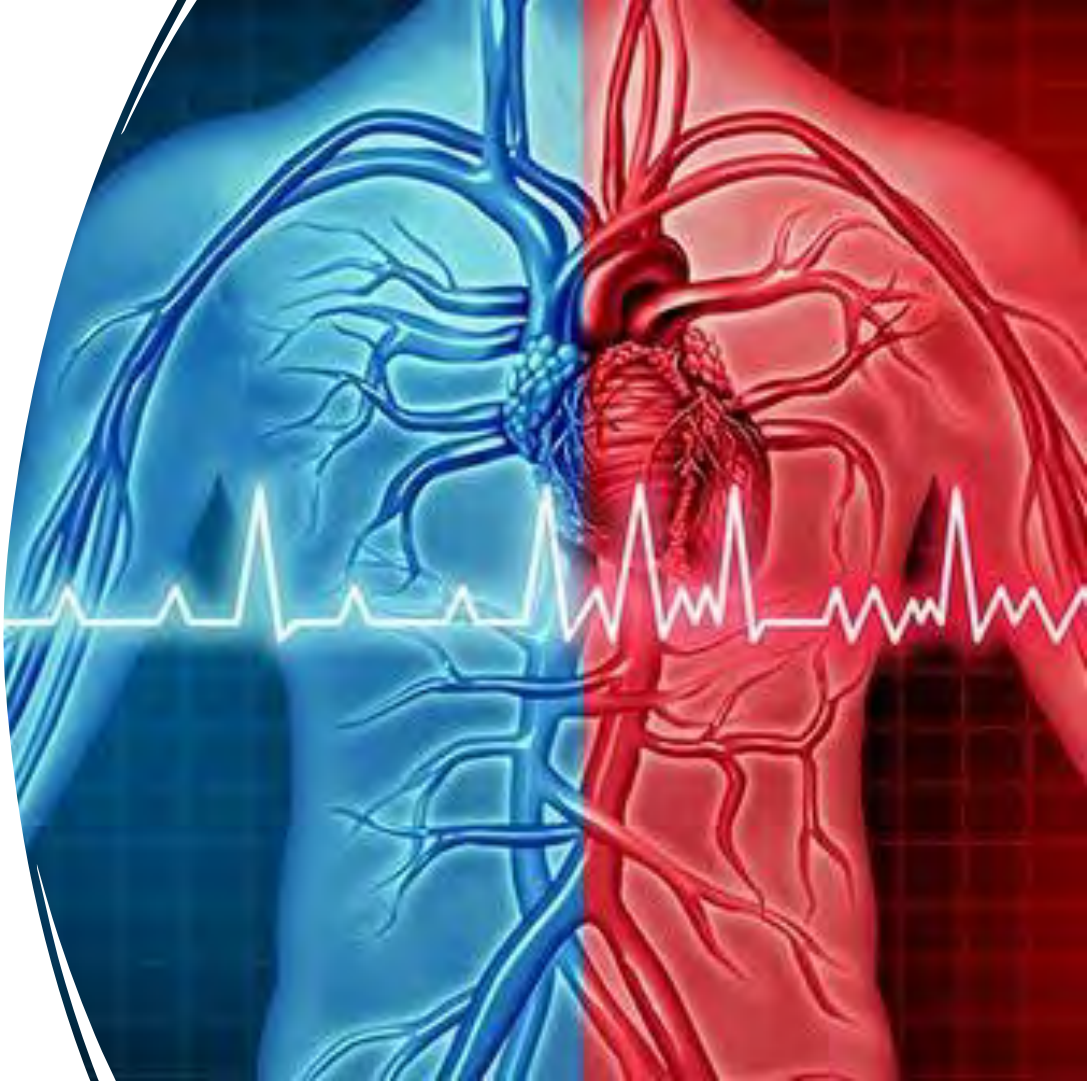
Checklist during follow-up of AF patients on NOACs

	Interval	Comments
Compliance	Each visit	Inspect remaining medication Stress importance of compliance Inform about compliance aids
Thrombo-embolism	Each visit	Cerebral, systemic and pulmonary circulation
Bleeding	Each visit	"Nuisance" bleeding – prevention possible? Bleeding with risk or impact on QoL – prevention possible? Need to revise dose?
Side effects	Each visit	Continuation? Temporary cessation with bridging? Change of anticoagulant drug?
Co-medications	Each visit	Prescription or over-the counter drugs? Even temporary use can be risky
Blood sampling	Yearly 6-monthly 3-monthly on indication	Haemoglobin, renal, liver function Renal function if CrCl 30-60 ml/min or if on dabigatran and aged >75 years or fragile If CrCl 15-30 ml/min If intercurring condition may impact renal or hepatic function.

Case Study



Lets introduce Doris

- 81 yr old
- Admission to A&E with SoB and irregular pulse – AF diagnosed
- PMH:
  - Hypertension
  - Angina
  - Osteoarthritis
- On examination:
  - 55kg
  - BP 130/80, HR 85 bpm - AF
  - SrCr 120, eGFR 52ml/min

Drugs on admission

- Aspirin 75mg daily
- Atorvastatin 20mg daily
- Amlodipine 5mg daily
- Indapamide 2.5mg daily

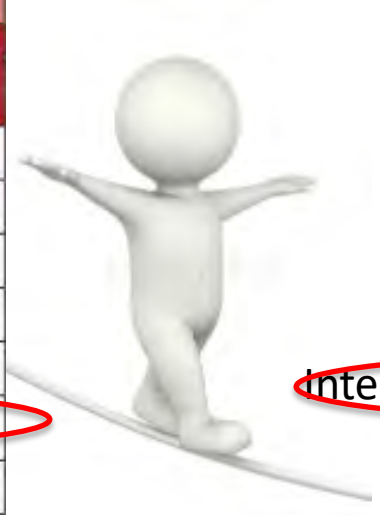
- fluconazole 50mg daily (for another 5 days)

- OTC medication:
  - Ibuprofen when required
  - Ginger, Ginko, Garlic

Should we anti coagulate?

CHA_2DS_2VASc

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	Patients (*n*=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%



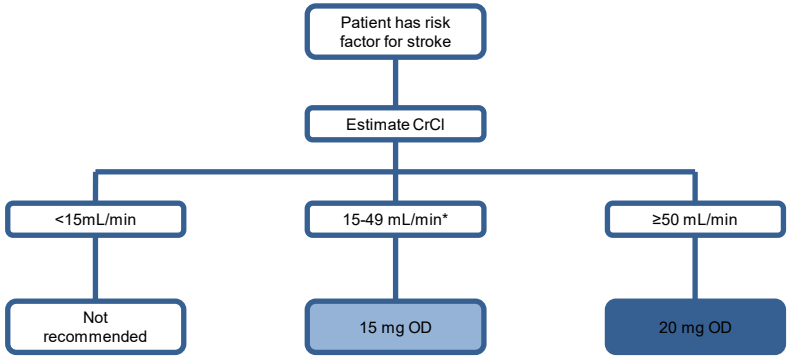
ORBIT

	Score	Bleeds per 100 patient-years
Low	0-2	2.4
Intermediate	3	4.7
High	4-7	8.1

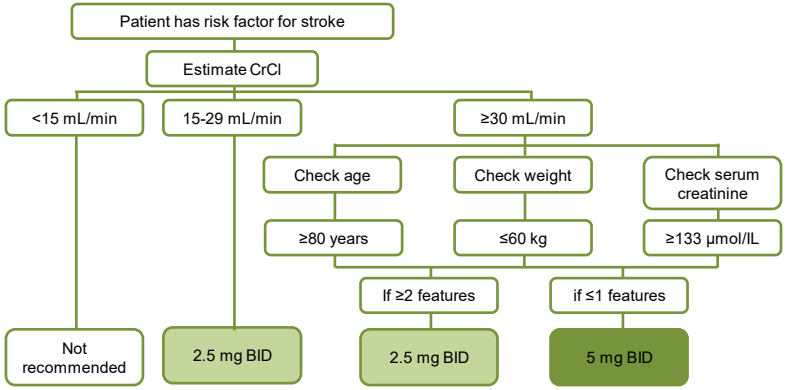
Dose adjustments in AF[1-4]

Refer to individual medicine SmPC's for dose reduction criteria

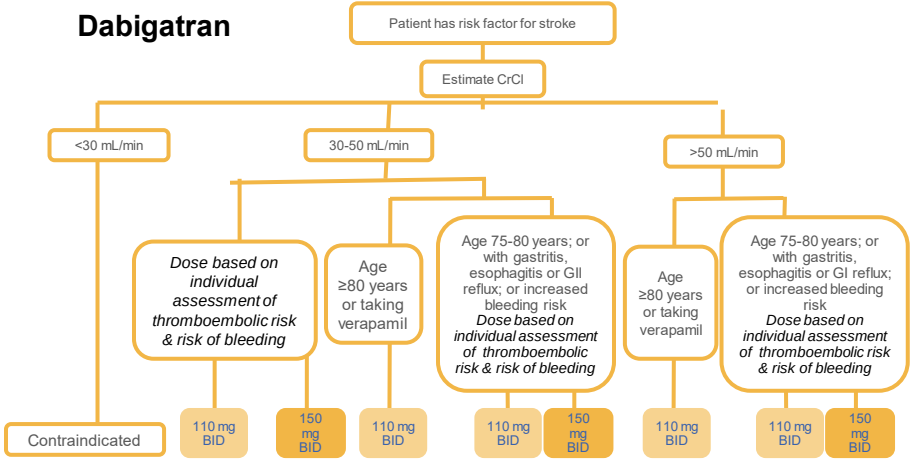
Rivaroxaban



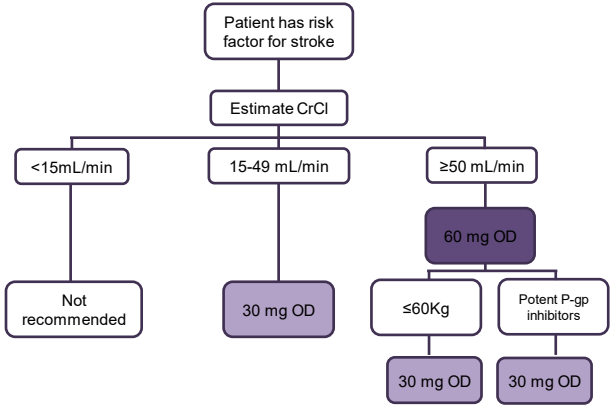
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

Aid memoir to dose reduction of NOACs

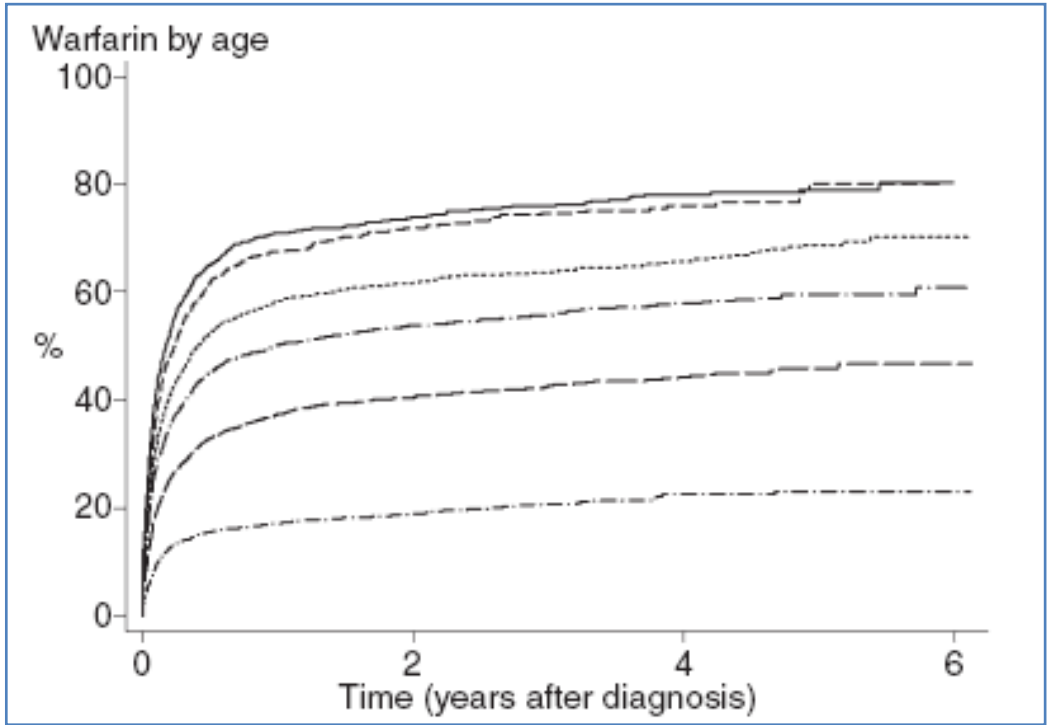
A Age

B Body weight

C Creatinine clearance

D Drugs

Older AF patients less likely to get warfarin



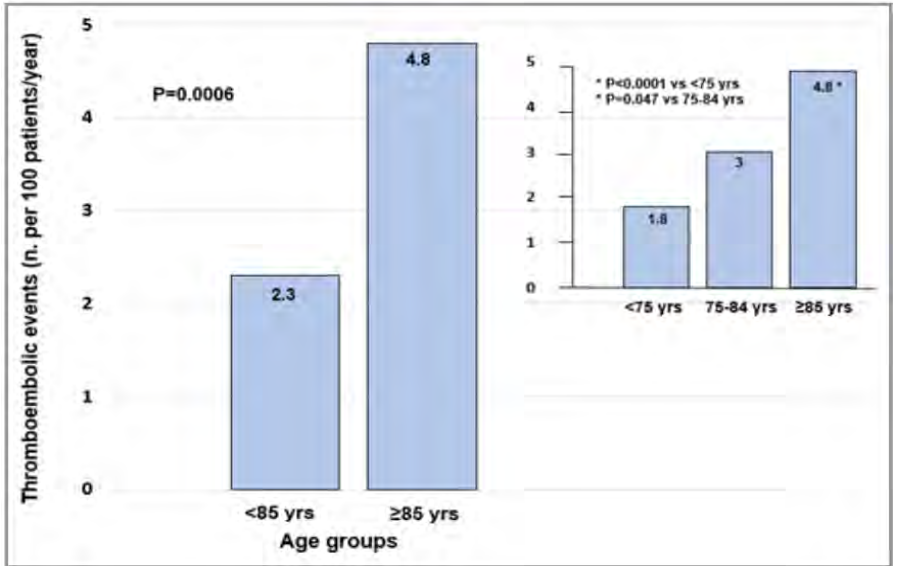
Younger

Older

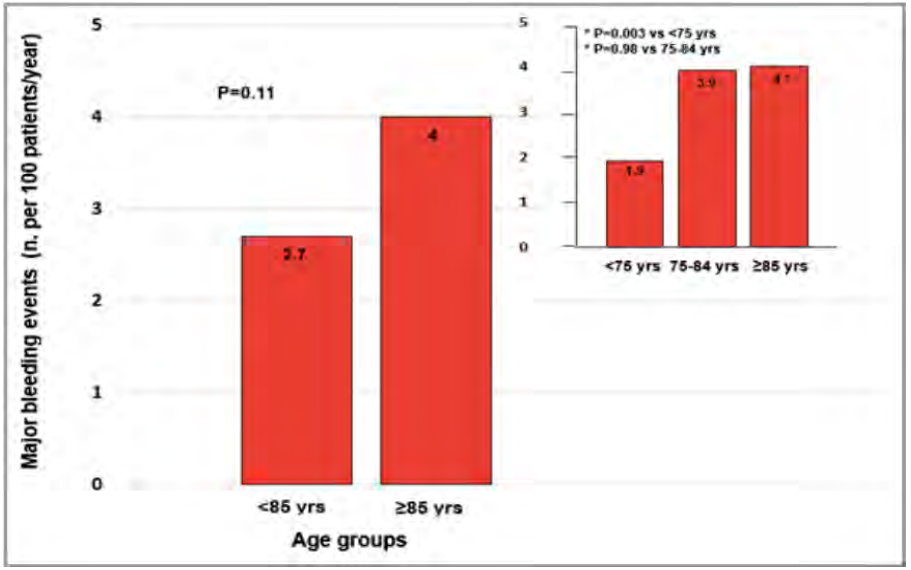
Gallagher AM *et al. J Thromb & Haem* 2008;6:1500-1506

Is age just a number?

Data from PREFER in AF
(PREvention oF thromboembolic events–European Registry in Atrial Fibrillation)



Incidence of thromboembolic events (stroke/TIA/systemic embolism) at 1 year in patients aged <85 and ≥85 years and rates of thromboembolic events according to 3 age strata (<75, 75–84, and ≥85 years)



Incidence of major bleeding at 1 year in patients aged <85 and ≥85 years and rates of major bleeding according to 3 age strata (<75, 75–84, and ≥85 years).

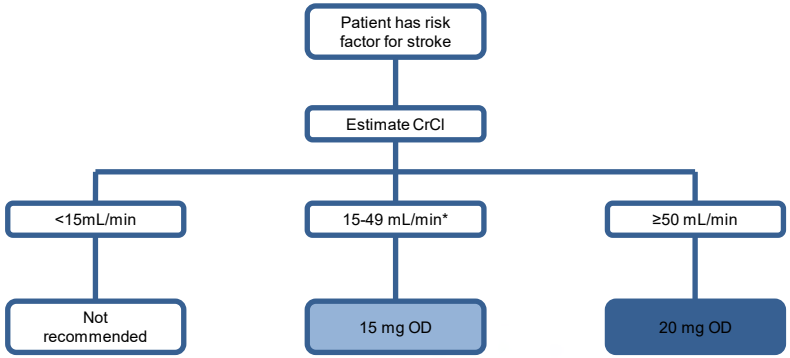
Ref: J Am Heart Assoc. 2017; 6:e005657

Dose adjustments in AF[1-4]

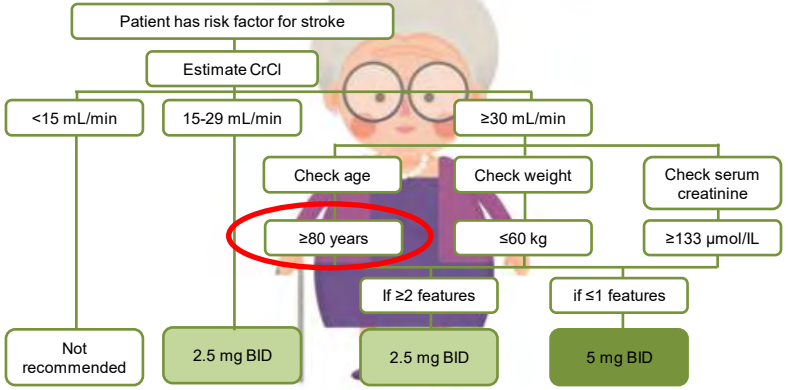
Refer to individual medicine SmPC's for dose reduction criteria

A - AGE

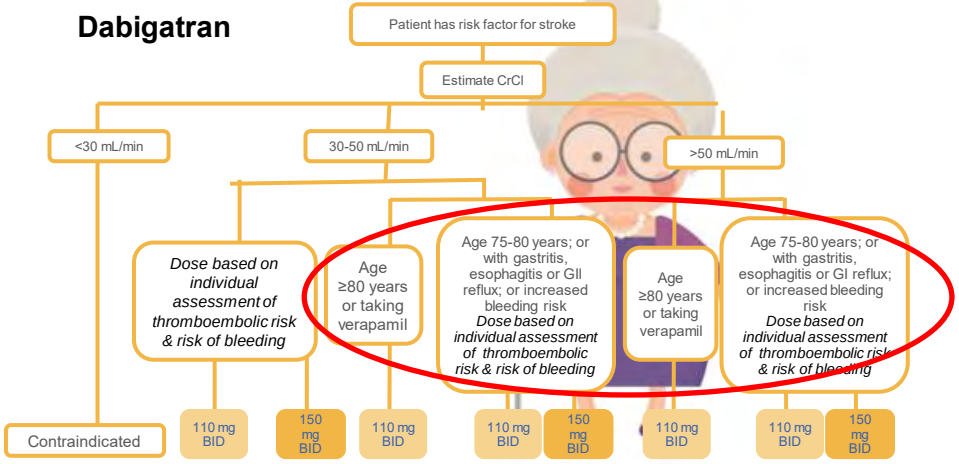
Rivaroxaban



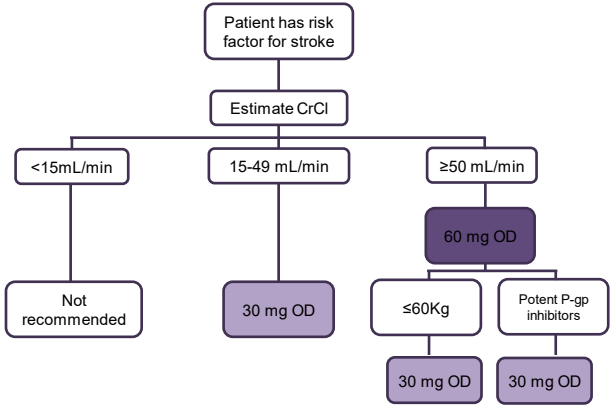
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

B – Body weight

- Weight at borderlines – 59kg to 61kg
- Which NOACs to dose reduce
- Study demonstrating increase bleed risk associated with lower body weight[1]
  - Consider dose reduction if BMI < 18.5kg/m^2

    (noting this may be unlicensed)

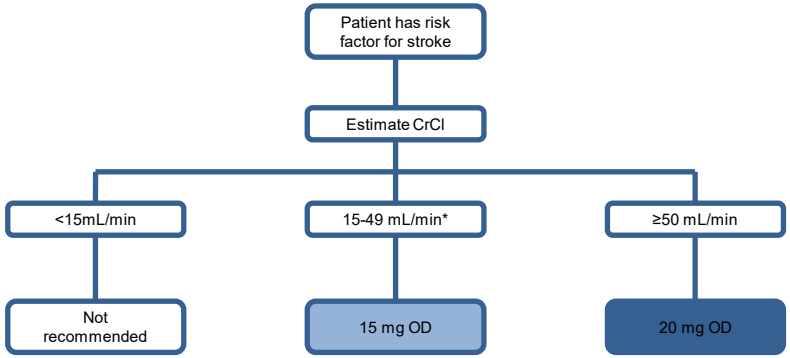
[1]Heart Rhythm http://dx.doi.org/10.1016/j.hrthm. 2016.12.036

Dose adjustments in AF[1-4]

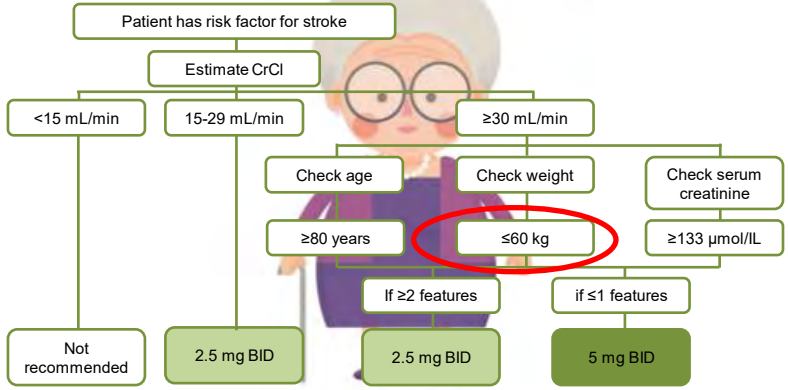
Refer to individual medicine SmPC's for dose reduction criteria

B - Body Weight

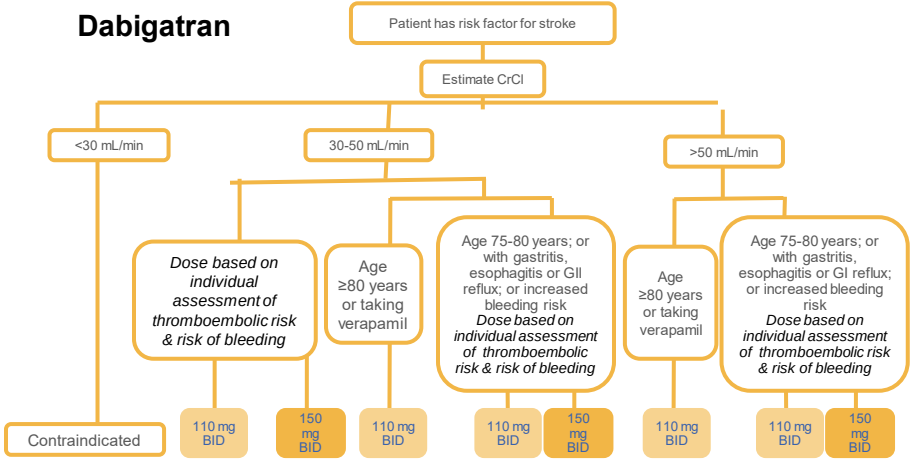
Rivaroxaban



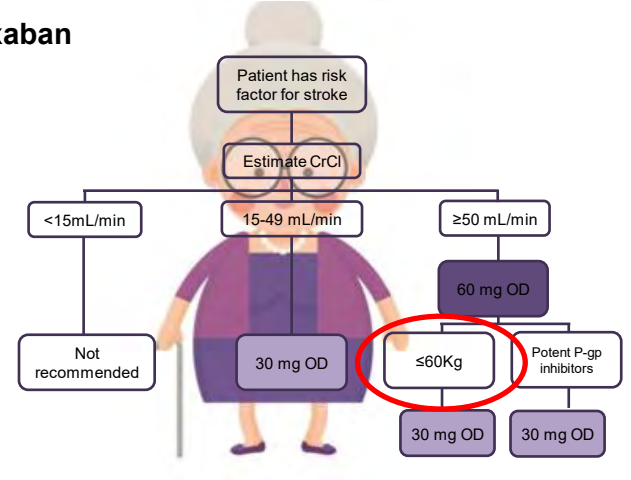
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

C – Creatinine clearance

Drug Safety Update

MHRA

Advice for healthcare professionals:

- MHRA has received reports and queries related to the choice of renal function estimate used when prescribing medicines for patients with renal impairment
- for most drugs and for most adult patients of average build and height, estimated Glomerular Filtration Rate (eGFR) should be used to determine dosage adjustments
- creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault formula (see below) to determine dosage adjustments for:
    - direct-acting oral anticoagulants (DOACs)

Ref: Drug Safety Update volume 13, issue 3: October 2019: 3

How to assess renal function?

- NOAC trials used CrCl to estimate renal function, hence SPCs recommend this method
- eGFR may overestimate for ages > 65yrs, CrCl may underestimate for ages >65yrs[1]
- Extremes of body weight can over/under estimate renal function

[1] MacCallum PK et al. BMJ Open 2013;3:e003343.

Calculating Creatinine Clearance

Cockcroft–Gault:

$$\frac{\text{CrCl} = \{(140 - \text{age}) * (\text{weight in kg}) * (F)\}}{\text{Serum creatinine}}$$

Where F = 1.23 if male or 1.04 if female

Calculating Creatinine Clearance

$$\text{Cockcroft–Gault: CrCl} = \frac{(140 - \text{age } 81) * (\text{weight in kg } 55) * (\text{F } 1.23)}{\text{Serum creatinine } 120}$$

Where F = 1.23 if male or 1.04 if female

- Age 81 years
- Female
- Serum creatinine 120 µmol/l
- Weight 55 kg
- Height 5 feet 7 inches (170 cm)
- ~~eGFR 52 ml/min~~

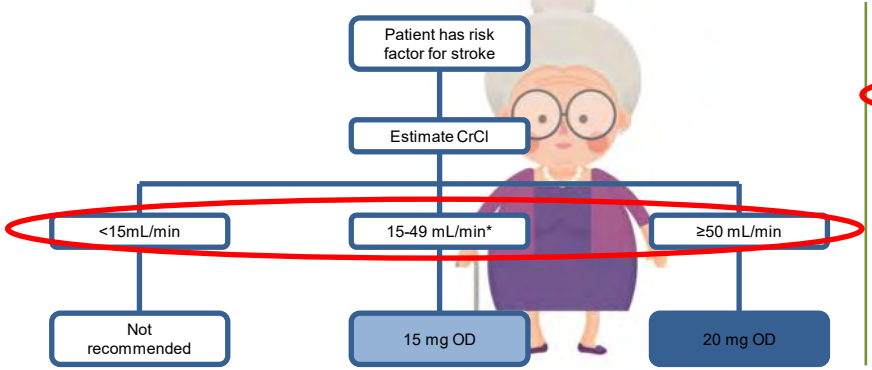
CrCl: using CG 33 ml/min

Dose adjustments in AF[1-4]

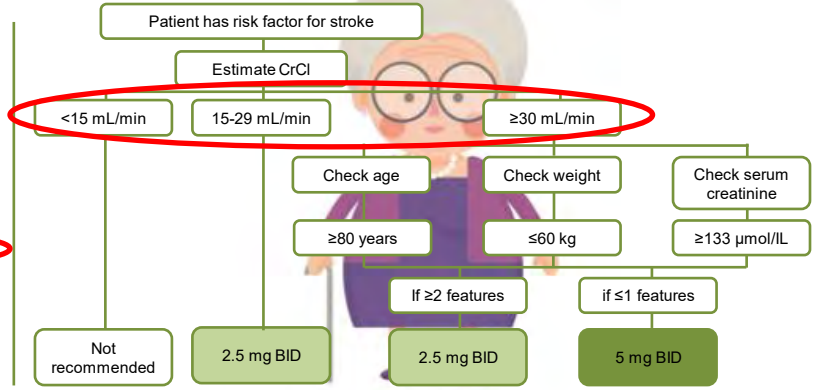
Refer to individual medicine SmPC's for dose reduction criteria

C - Creatinine clearance

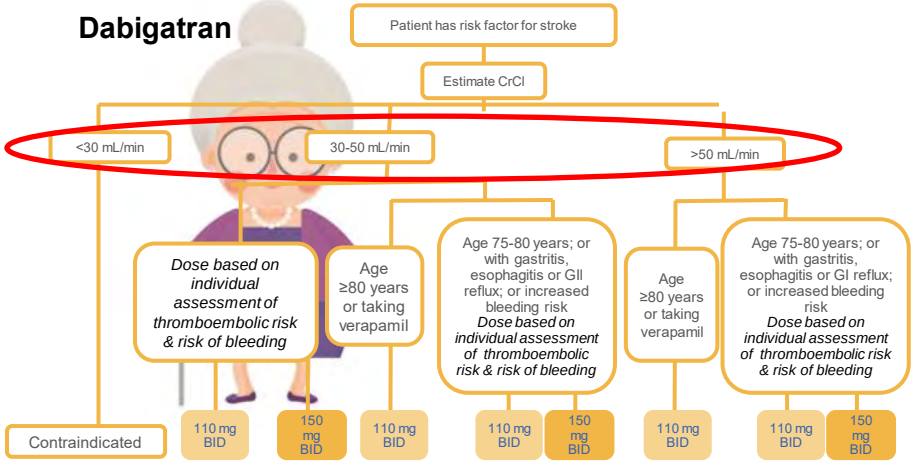
Rivaroxaban



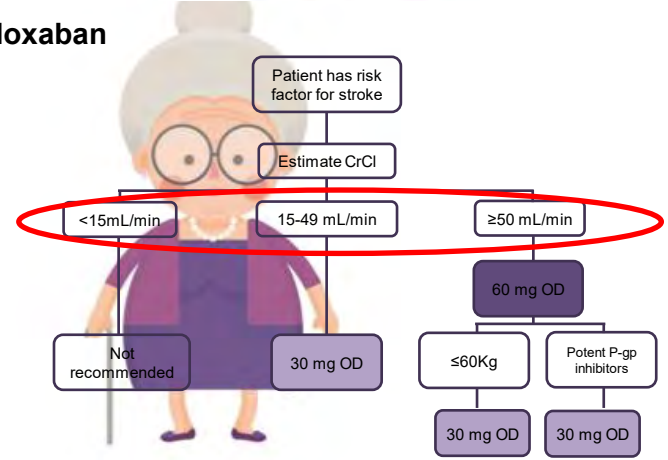
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

D - Drug Interactions

1. Pharmacodynamic (functional) interactions
   - Enhance the physiological affects through synergistic impact
   - Any antithrombotic drug or drug that increases bleeding risk

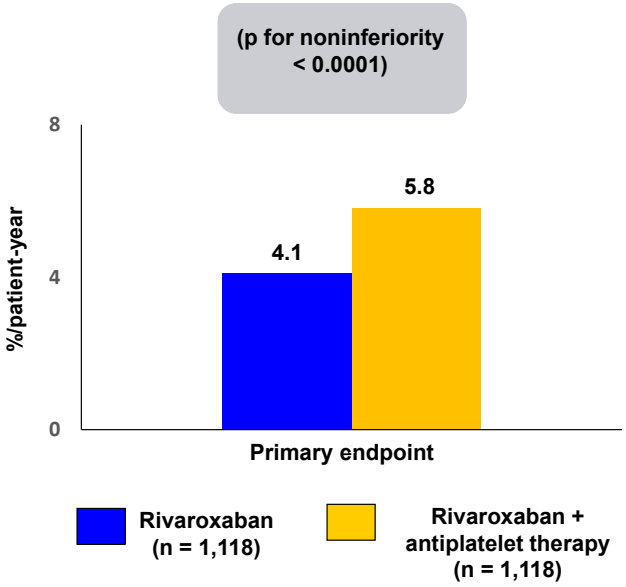
2. Phamacokinetic interactions
   - Drugs that increase or decrease drug exposure
   - Inhibitors or inducers of P-glycoprotein

AFIRE

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with atrial fibrillation and stable coronary artery disease were randomized to rivaroxaban 15 mg daily (10 mg daily for creatine clearance 15-49 ml/min) versus rivaroxaban/antiplatelet therapy.



RESULTS

- Primary efficacy endpoint: all-cause mortality, myocardial infarction, stroke, unstable angina requiring revascularization, or systemic embolism occurred in 4.1%/patient-year in the rivaroxaban monotherapy group compared with 5.8%/patient-year in the rivaroxaban/antiplatelet therapy group (p for noninferiority < 0.0001)
- Primary safety endpoint: major bleeding (ISTH criteria) occurred in 1.6%/patient-year in the rivaroxaban monotherapy group compared with 2.8%/patient-year in the rivaroxaban/antiplatelet therapy group (p = 0.01)

CONCLUSIONS

- Among patients with atrial fibrillation and stable coronary artery disease, rivaroxaban monotherapy vs. rivaroxaban/antiplatelet therapy was noninferior for ischemia and superior for bleeding

Yasuda S, et al. N Engl J Med 2019;Sep 2:[Epub]

Drug–drug interactions with NOACs

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ('area under the curve')

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 × 75 mg if CrCl 30–50 mL/min)	+100%[138]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPC]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC
Others					
Naproxen	P-gp competition; pharmacodynamically increased bleeding time	No data yet	+55%[139]	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[SmPc]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/CYP2J2 inducers				

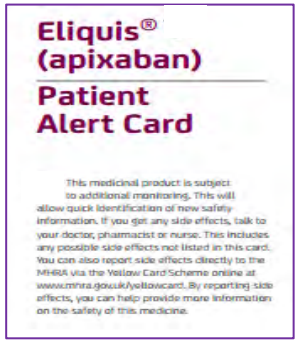
Taken from:
The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation 2018. European Heart Journal (2018) 39, 1330–1393

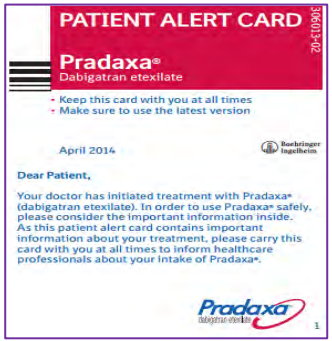
Accessed (in Feb 2020) at: https://www.escardio.org/Guidelines/Recommended-Reading/Heart-Rhythm/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation

Other considerations for reducing bleeding risk

Patient Alert Cards - audit

- Anticoagulated patients should carry their alert card at all times
- Alert cards are included as part of patient guides
- Do all your patients have them?





When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban		Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 50–80 ml/min	≥36h	≥72h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 30–50 ml/min §	≥48h	≥96h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 15–30 ml/min §	not indicated	not indicated	≥36h	≥48h	no data yet	no data yet	≥36h	≥48h
CrCl <15 ml/min	no official indication for use							

Low risk: surgery with low risk of bleeding. High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).

Final review for Doris

- 81 yr old
- Admission to A&E with SoB and irregular pulse – AF diagnosed
- PMH:
  - Hypertension
  - Angina
  - Osteoarthritis
- On examination:
  - 55kg
  - BP 130/80, HR 85 bpm - AF
  - SrCr 120, eGFR 52ml/min

Drugs on admission

- Aspirin 75mg daily
- Atorvastatin 20mg daily
- Amlodipine 5mg daily
- Indapamide 2.5mg daily

- fluconazole 50mg daily (for another 5 days)

- OTC medication:
  - Ibuprofen when required
  - Ginger, Ginko, Garlic

Take home message

Factors associated with increased bleeding risks with anticoagulation use:

- Remember your ABCD
  - ❑AGE
    - ❑BODY WEIGHT
      - ❑CREATINE CLEARANCE
        - ❑DRUGS

Questions

Atrial fibrillation and anticoagulation

Paul Wright MRPharmS (consultant) MSc IPresc

Consultant Cardiac Pharmacist

Barts Health NHS Trust

Twitter: @pharmBHC