

AF-related stroke risk and the impact of treatments



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Heart Rhythm Congress
AF Association Patients Day

The ICC, Birmingham, UK
Sunday 9th October 2016

Declarations:

Advisory board meetings;

Novartis

Boehringer Ingelheim

Astra-Zeneca

Bayer

Daiichi Sankyo

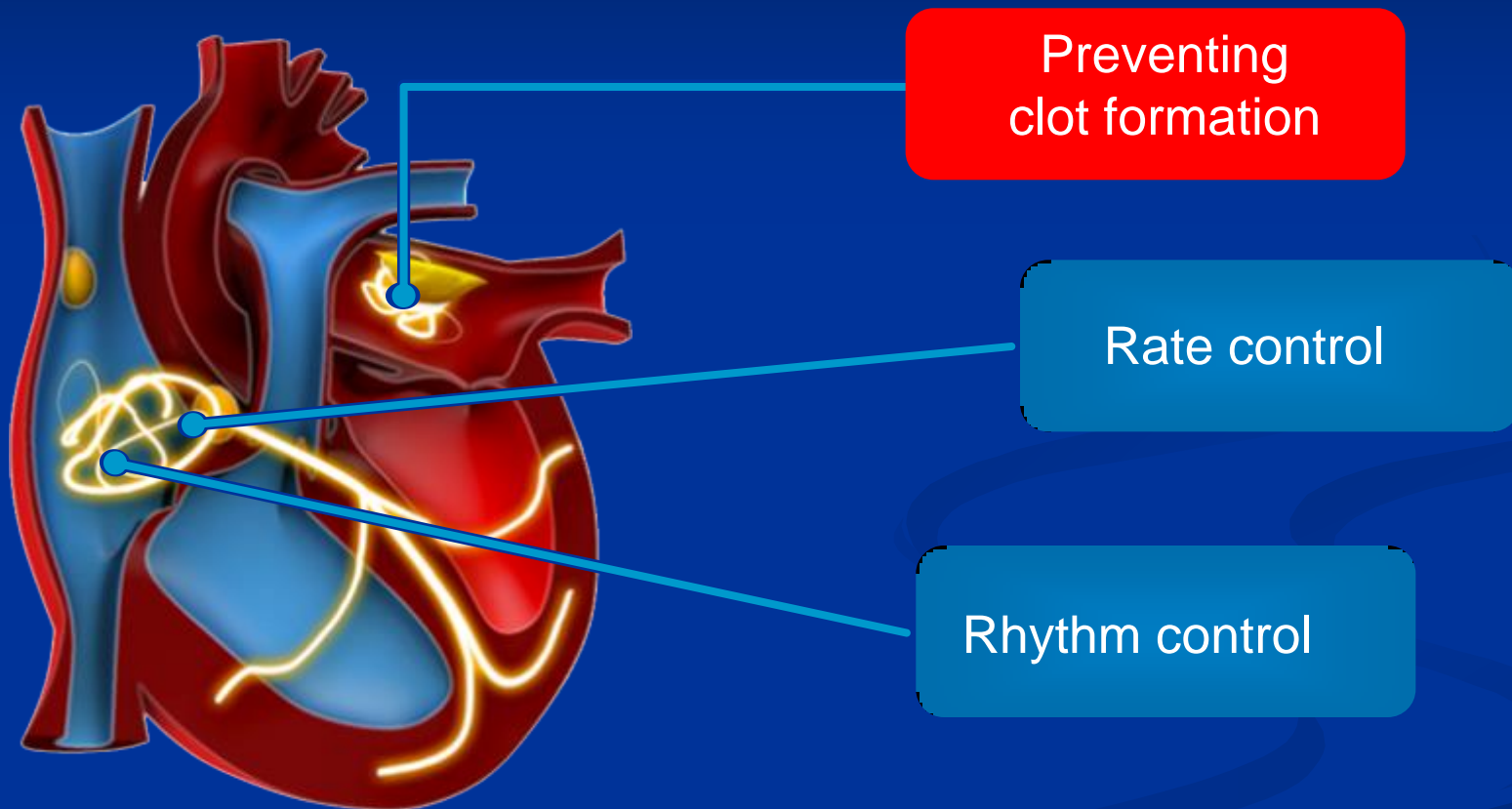
Pfizer

Vifor

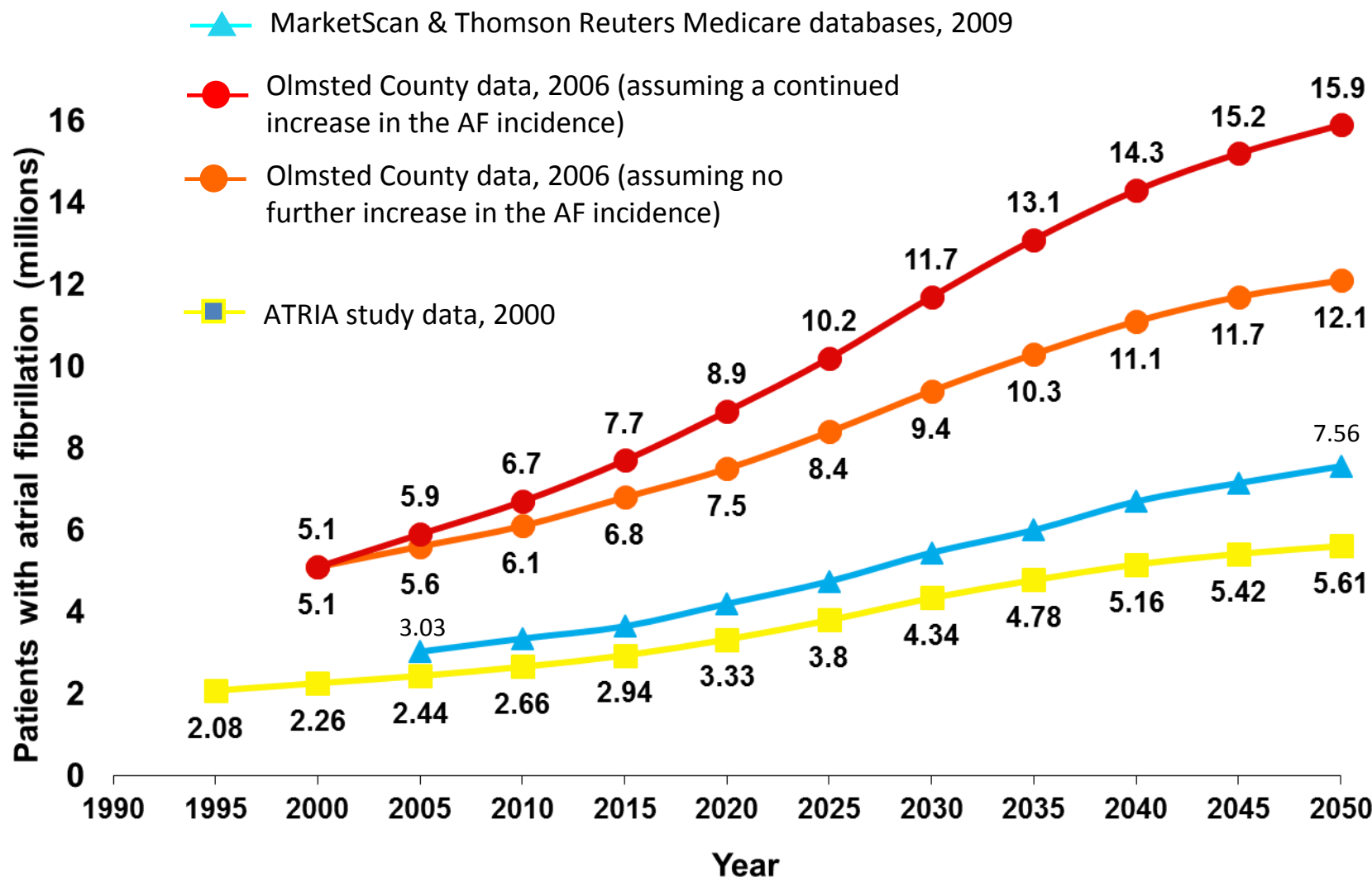
Role of Primary Care in AF management

- Opportunistic screening
- Stroke Risk assessment
- Reducing Stroke Risk
- GRASP-AF
- Determining an appropriate treatment strategy;
- Rate v Rhythm control
- Patient Education & Information

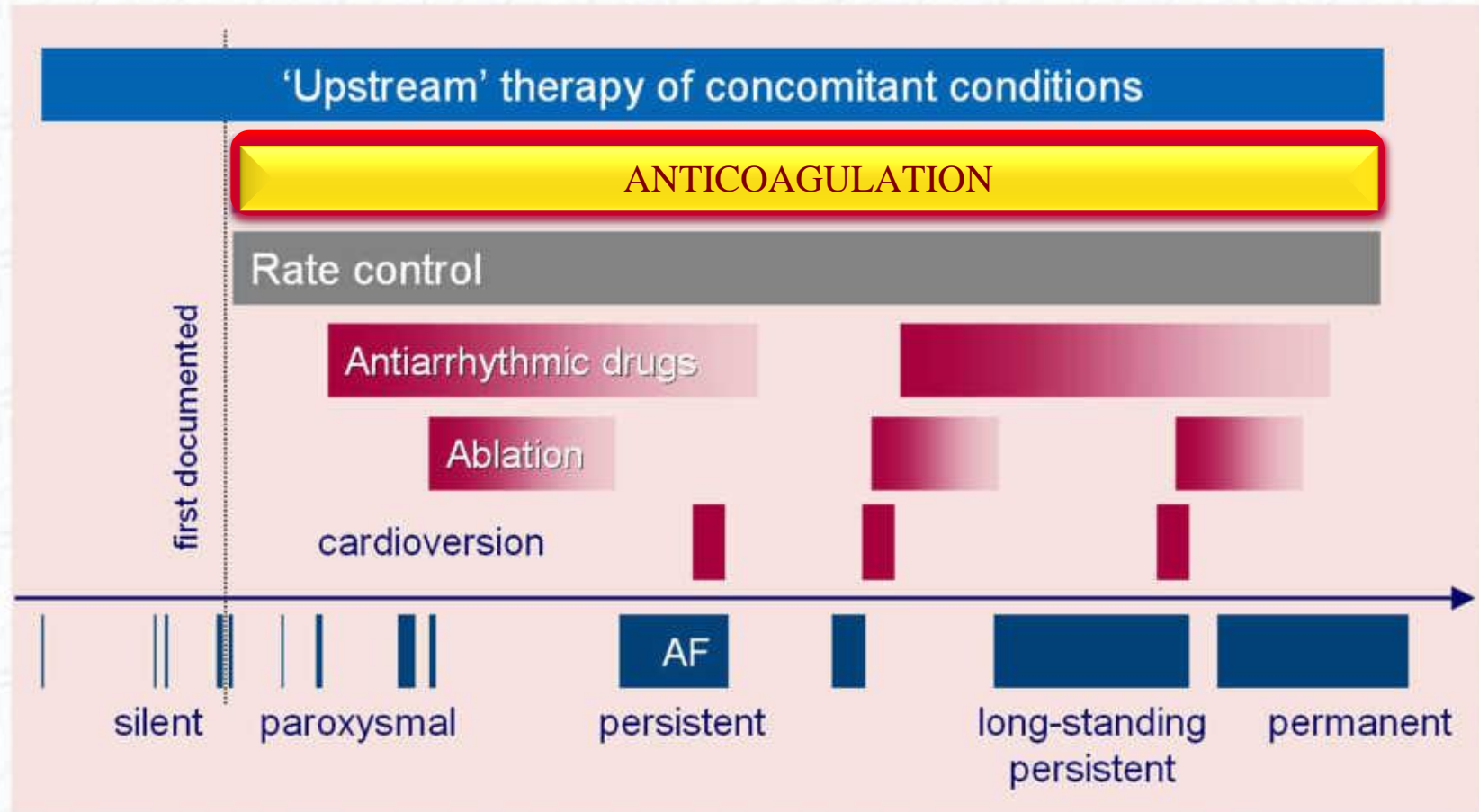
Aims of treatment



Projected Number of Patients With AF by 2050



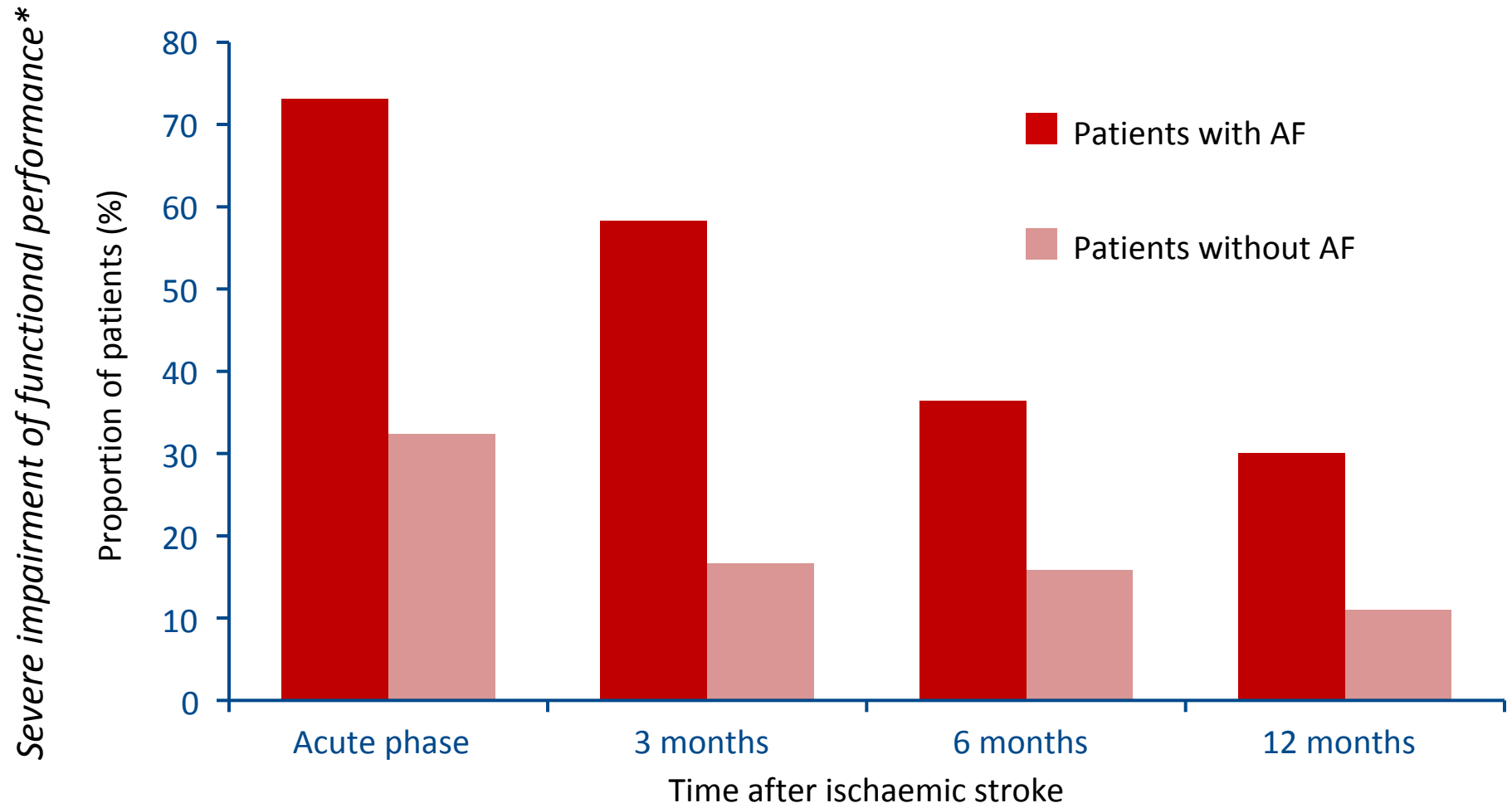
Natural time course of AF



AF = atrial fibrillation

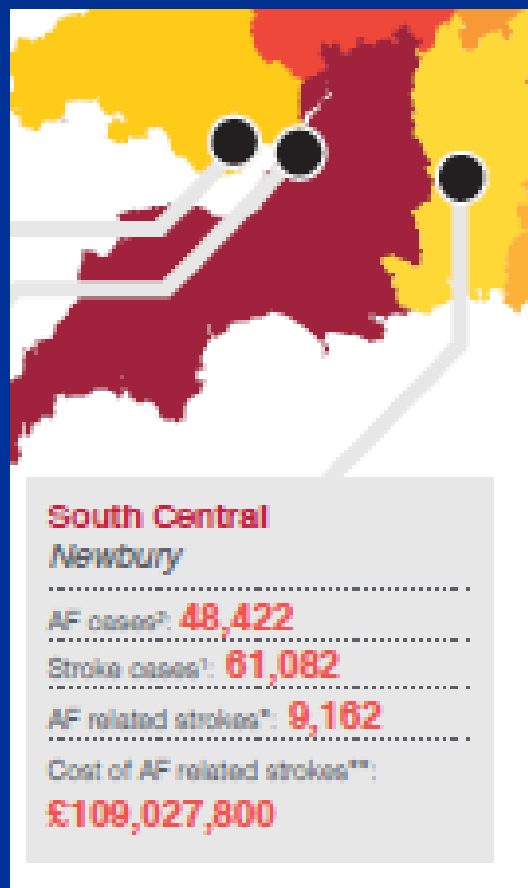
Stroke prevention

AF is associated with **poorer functional performance** in survivors of ischaemic stroke



>40-year follow-up of 5070 participants in the Framingham study; *Barthel Index

The SAFE Report



AF and Stroke: The UK at a Glance

This map is designed to provide a general overview of AF and stroke cases in the UK and figures are based on various estimations and assumptions.

1. Scarborough P et al. Stroke statistics 2009 British Heart Foundation Health Promotion Research Group. <http://www.bhf.org.uk/research/statistics/heart-statistics-publications.aspx>, accessed May 2012
2. National Institute for Health and Clinical Excellence. Guideline 36. Coding template. Atrial Fibrillation: The management of atrial fibrillation. July 2006, available at <http://www.nice.org.uk/uksgg/guidance/implementationtool/codingtemplate>, accessed June 2012
3. GSA Level 2 QI Index 2010/11 <http://www.ic.nhs.uk/statistics-and-data-collections/supporting-information/audit-and-performance/the-quality-and-outcomes-framework/qof-2010-11/qof-2010-11-data-tables/qof-prevalence-data-tables-2010-11>, accessed June 2012
4. <http://www.scotland.gov.uk/Publications/2009/11/09151450>
5. http://www.atrialfoundation.org.uk/files/Healthcare20CentresAF%20reports20Wales_v1_singles.pdf
6. QOF Data2008-10. Department of Health, Social Services and Public Safety. Available online at http://www.dhsp.gov.uk/central_forbidden_indicators_bq_tag.pdf (accessed 15 June 2011)
7. <http://www.nhs.uk/press-releases/7-nh-chest-heart-and-stroke-welcome-fast-campaign>

Northern Ireland *Belfast*

AF cases¹: **24,000**

Stroke cases¹: **3,000**

AF related strokes²: **450**

Cost of AF related strokes³:
£5,355,000

North West *Manchester*

AF cases¹: **87,397**

Stroke cases¹: **130,803**

AF related strokes²: **19,620**

Cost of AF related strokes³:
£233,478,000

West Midlands *Birmingham*

AF cases¹: **68,094**

Stroke cases¹: **94,644**

AF related strokes²: **14,197**

Cost of AF related strokes³:
£168,944,300

Wales *Cardiff*

AF cases¹: **50,138**

Stroke cases¹: **61,448**

AF related strokes²: **9,217**

Cost of AF related strokes³:
£109,682,300

South West *Bristol*

AF cases¹: **75,019**

Stroke cases¹: **100,348**

AF related strokes²: **15,052**

Cost of AF related strokes³:
£179,118,800

South Central *Newbury*

AF cases¹: **48,422**

Stroke cases¹: **61,082**

AF related strokes²: **9,162**

Cost of AF related strokes³:
£109,027,800

South East Coast *Horley*

AF cases¹: **59,520**

Stroke cases¹: **72,579**

AF related strokes²: **10,887**

Cost of AF related strokes³:
£129,555,300

Scotland *Edinburgh*

AF cases¹: **60,074** (over 40s)

Stroke cases¹: **95,959**

AF related strokes²: **14,394**

Cost of AF related strokes³:
£171,288,600

North East *Newcastle Upon Tyne*

AF cases¹: **33,394**

Stroke cases¹: **55,828**

AF related strokes²: **8,374**

Cost of AF related strokes³:
£99,650,600

Yorkshire and the Humber *Leeds*

AF cases¹: **64,922**

Stroke cases¹: **98,340**

AF related strokes²: **14,751**

Cost of AF related strokes³:
£175,536,900

East Midlands *Nottingham*

AF cases¹: **73,708**

Stroke cases¹: **74,563**

AF related strokes²: **11,184**

Cost of AF related strokes³:
£133,089,600

East of England *Cambridge*

AF cases¹: **91,944**

Stroke cases¹: **89,178**

AF related strokes²: **13,377**

Cost of AF related strokes³:
£159,186,300

London *London*

AF cases¹: **42,272**

Stroke cases¹: **85,508**

AF related strokes²: **12,826**

Cost of AF related strokes³:
£152,629,400

Atrial fibrillation: the management of atrial fibrillation

Issued: June 2014

NICE clinical guideline 180
guidance.nice.org.uk/cg180

NICE has accredited the process used by the Centre for Clinical Practice at NICE to produce guidelines. Accreditation is valid for 5 years from September 2009 and applies to guidelines produced since April 2007 using the processes described in NICE's 'The guidelines manual' (2007, updated 2009). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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NICE – Atrial Fibrillation

Key Priorities for implementation

- Personalised package of care and information
- Assessment of stroke and bleeding risks
- Interventions to prevent stroke

Personalised package of care

- offer people with AF a *personalised package of care*
 - *Stroke awareness and measures to prevent stroke*
 - Rate control
 - Assessment of symptoms for rhythm control
 - Who to contact for advice if needed
 - Psychological support if required

Assessing Stroke Risk

Guidelines – refining stroke risk assessment

CHA ₂ DS ₂ -VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex category (i.e. female gender)	1

CHA ₂ DS ₂ -VASc total score	Rate of stroke/other TE (%/year)*
0	0.0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	10.7
9	15.2

* Theoretical rates without therapy: assuming that warfarin provides a 64% relative reduction in TE risk (2.7% ARR), based on Hart *et al.* TE = thromboembolism

1 Lip GYH *et al.* *Stroke* 2010;41:2731–2738.

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

GRASP – AF



An automated tool to identify patients at high risk of stroke in AF and not on adequate thromboprophylaxis, using existing GP data



Delivered by PRIMIS+ and available via your Cardiac Network.

PRIMIS+



Audit of Atrial Fibrillation & CHADS2-VASc Scores

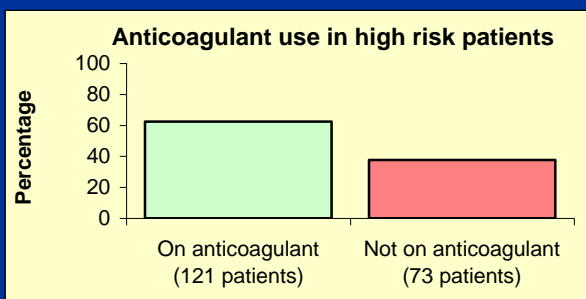
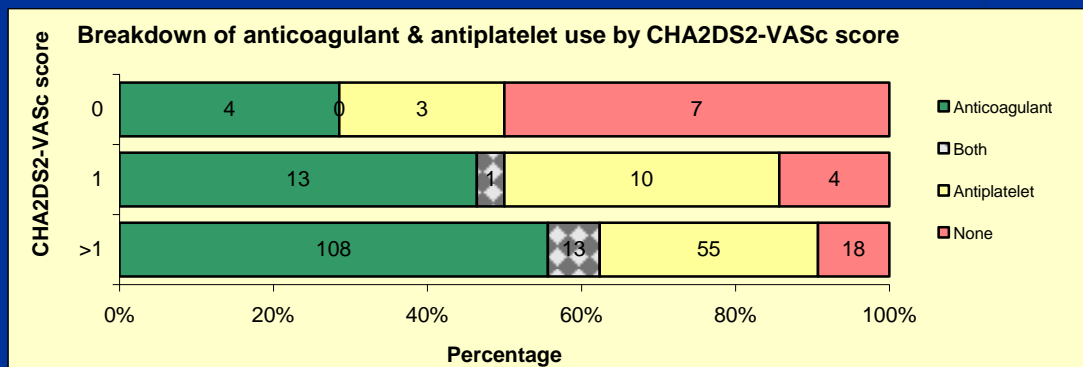
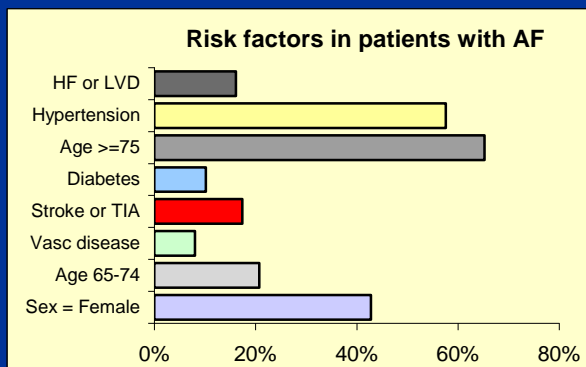
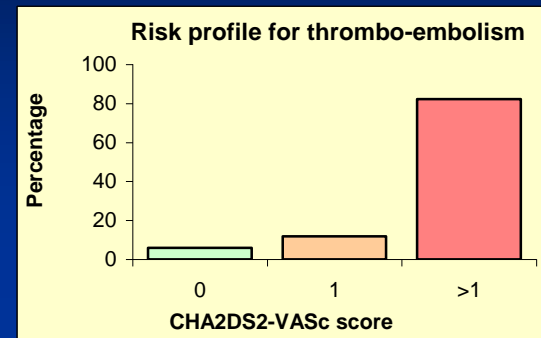
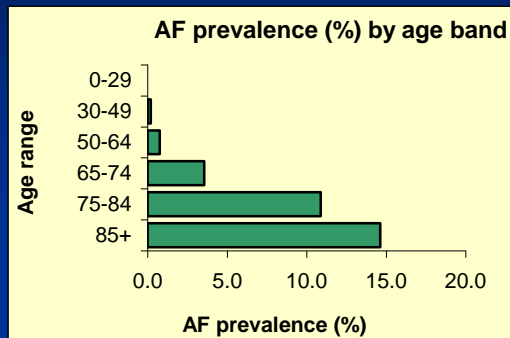
Select Risk Score **CHADS2-VASc** ▼

Practice:

Total Practice Population 15148

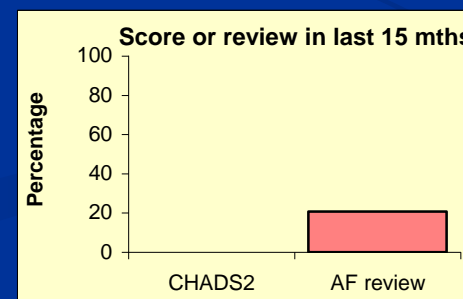
	Total	Percent
No. with Atrial Fibrillation	236	1.56
Age >= 65 yrs with AF	203	7.62

NB: Handling of anticoagulant exclusions



Strokes expected annually in the 73 high risk untreated

2.9

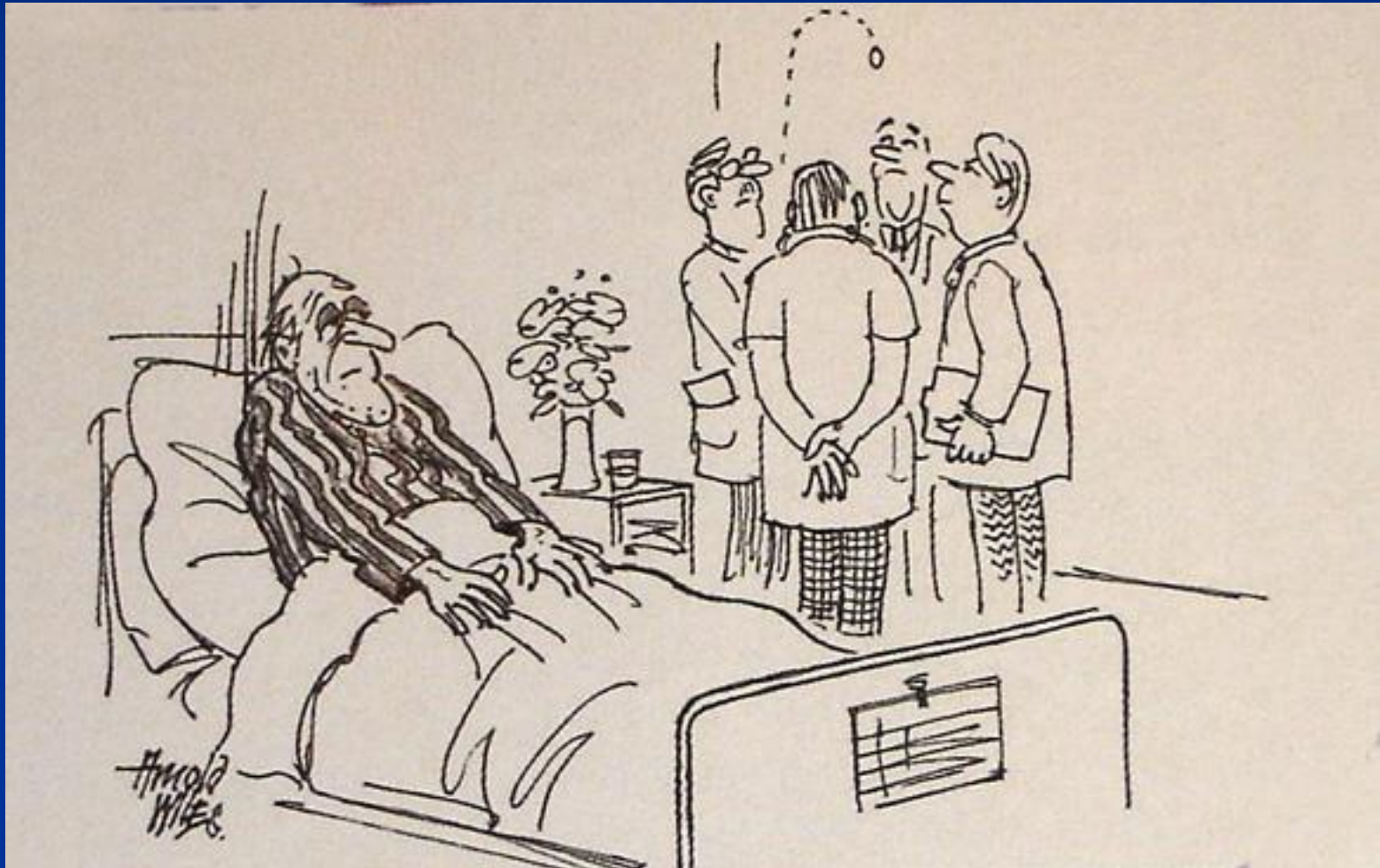


[Classic View](#)

[HELP](#)
[OVERVIEW](#)
[PODCAST](#)

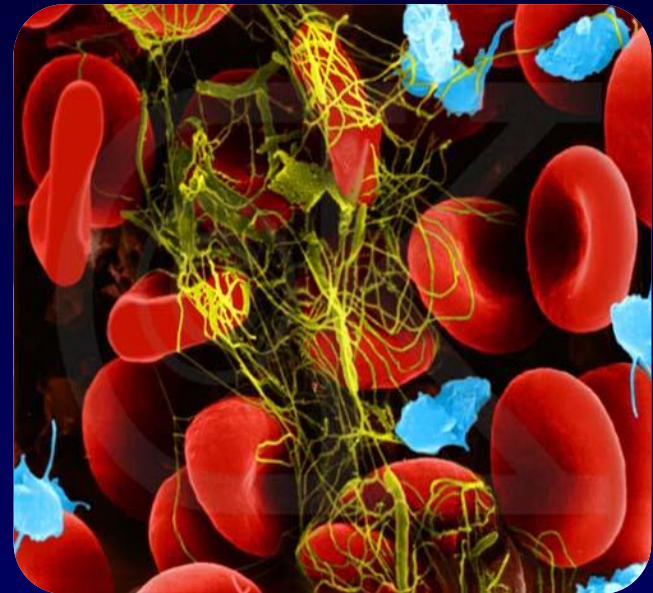
Stroke prevention Treatment

Warfarin or aspirin...?



Not all clots are the same

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



ridge.icu.ac.jp

Drug treatments to prevent stroke

- Do not offer stroke prevention treatment to people aged under 65 years with no risk factors other than their sex
- i.e. CHADS-VASc score 0 (men) or 1 (women)

Consider anticoagulation for men with a
CHADS-VASc score of 1

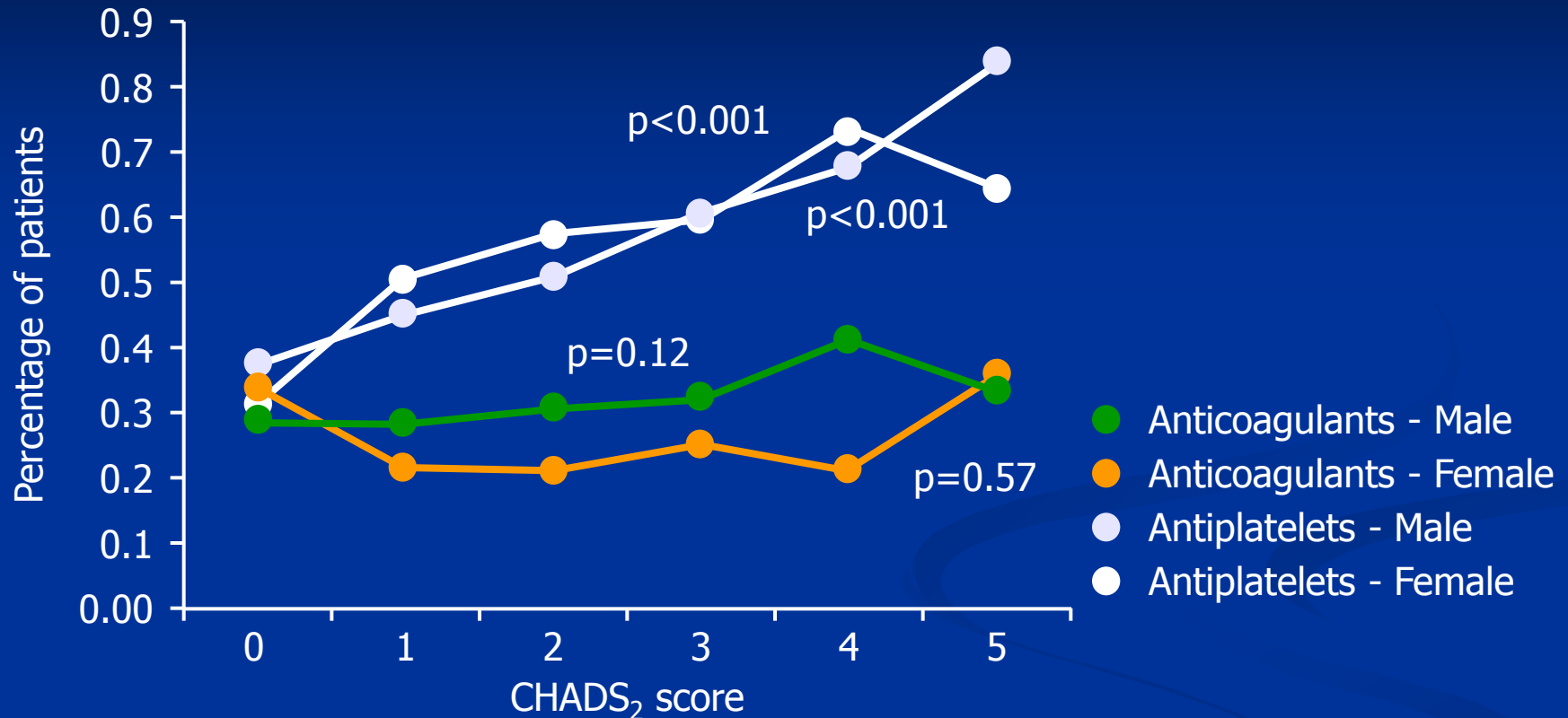
Offer anticoagulation to people with a
CHADS-VASc of 2 or above

Drug treatments to prevent stroke

- Discuss options for anticoagulation with the person and base choice on their clinical features and preferences

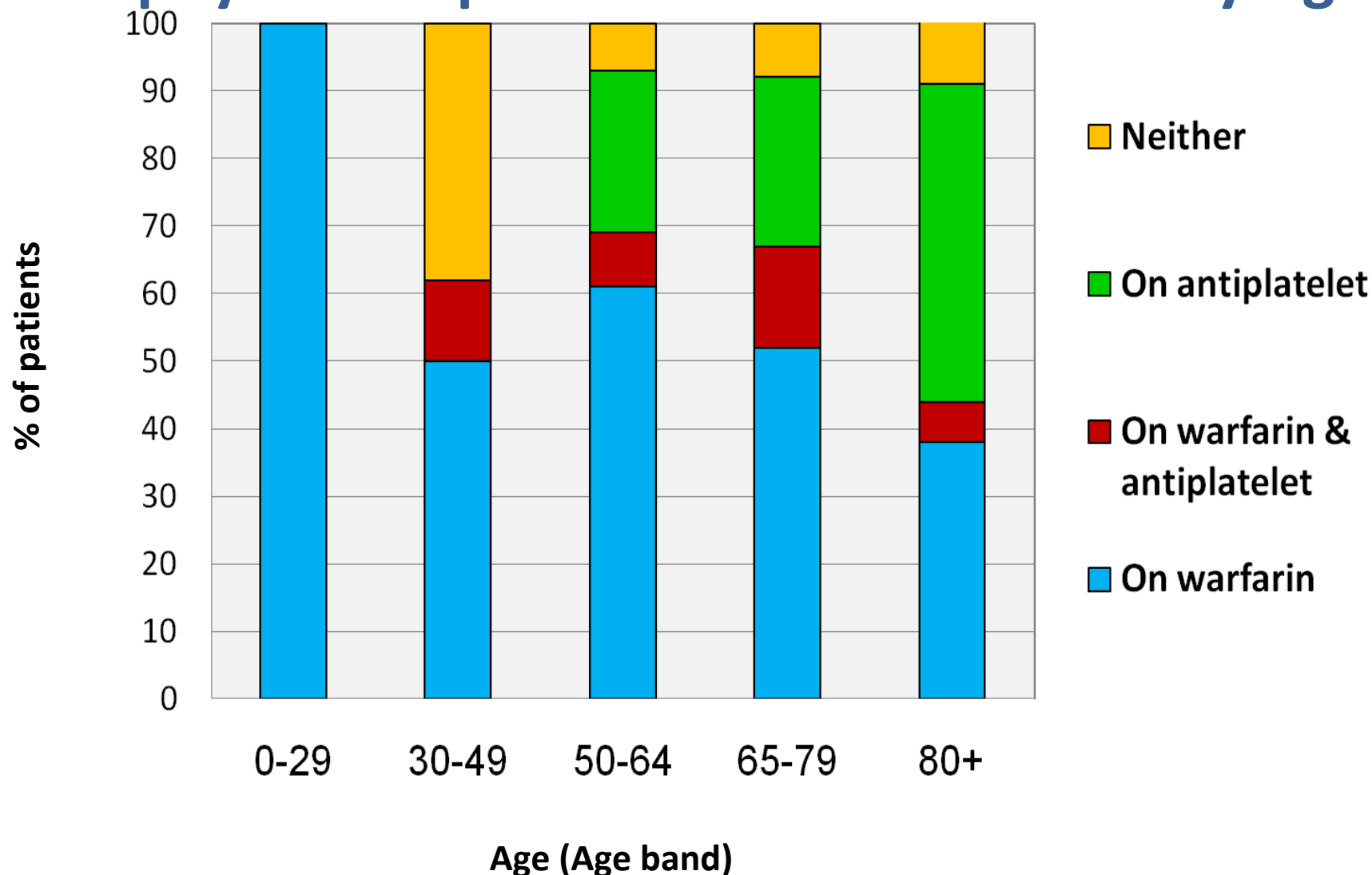
Do not offer Aspirin monotherapy solely for stroke prevention to people with atrial fibrillation

As stroke risk increases, so does aspirin use



- 52% of patients with AF are treated with antiplatelet treatment such as aspirin (1796/3483)
- Prescription of aspirin increases steeply with increasing CHADS₂ score

Prophylaxis of patients with CHADS2 >1 by Age



NICE National Institute for
Health and Care Excellence

**Atrial fibrillation: the management
of atrial fibrillation**

Issued: June 2014

NICE clinical guideline 180
guidance.nice.org.uk/cg180

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NICE estimate that in England:

- 191,500 people with AF are receiving oral anticoagulants

BUT

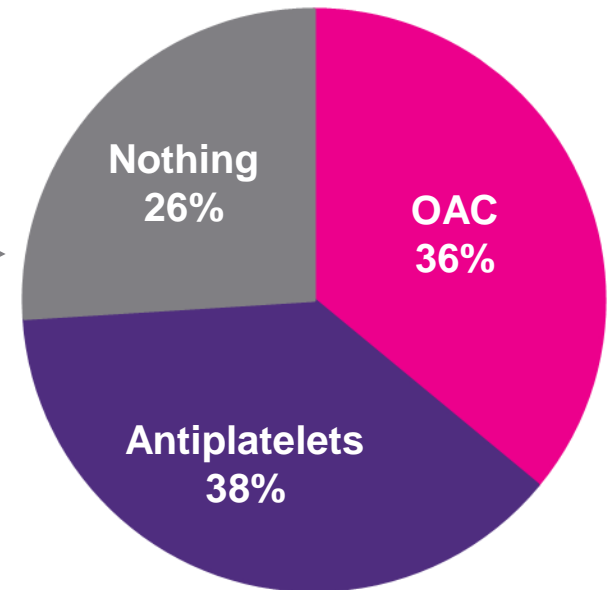
- 234,000 people with AF are receiving aspirin!

“By reviewing all AF patients at risk of stroke currently receiving aspirin, to see if they are appropriate for oral anticoagulation, we could prevent 5,000 strokes a year”

Sentinel Stroke National Audit Programme of the Royal College of Physicians*

Jan - March 2013
England, Wales, Northern
Ireland
11,939 stroke admissions

2,465 in AF



*www.rcplondon.ac.uk

NICE AF Guideline June
2014

Guidelines

Europe/America

What do other Guidelines tell us...?

Risk category	CHA ₂ DS ₂ -VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥2	Oral anticoagulant (OAC)
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin

What do other Guidelines tell us...?

Patient features	Recommended antithrombotic therapy
Low risk of stroke (eg, CHADS ₂ = 0)	None (rather than antithrombotic therapy)
Intermediate risk of stroke (eg, CHADS ₂ = 1)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel))
High risk of stroke (eg, CHADS ₂ = 2)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel)
Previous stroke/TIA	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel)

2012 ACCP guidelines

You JY et al. Chest 2012;141:e531S–e575S

Anticoagulation

Drug treatments to prevent stroke

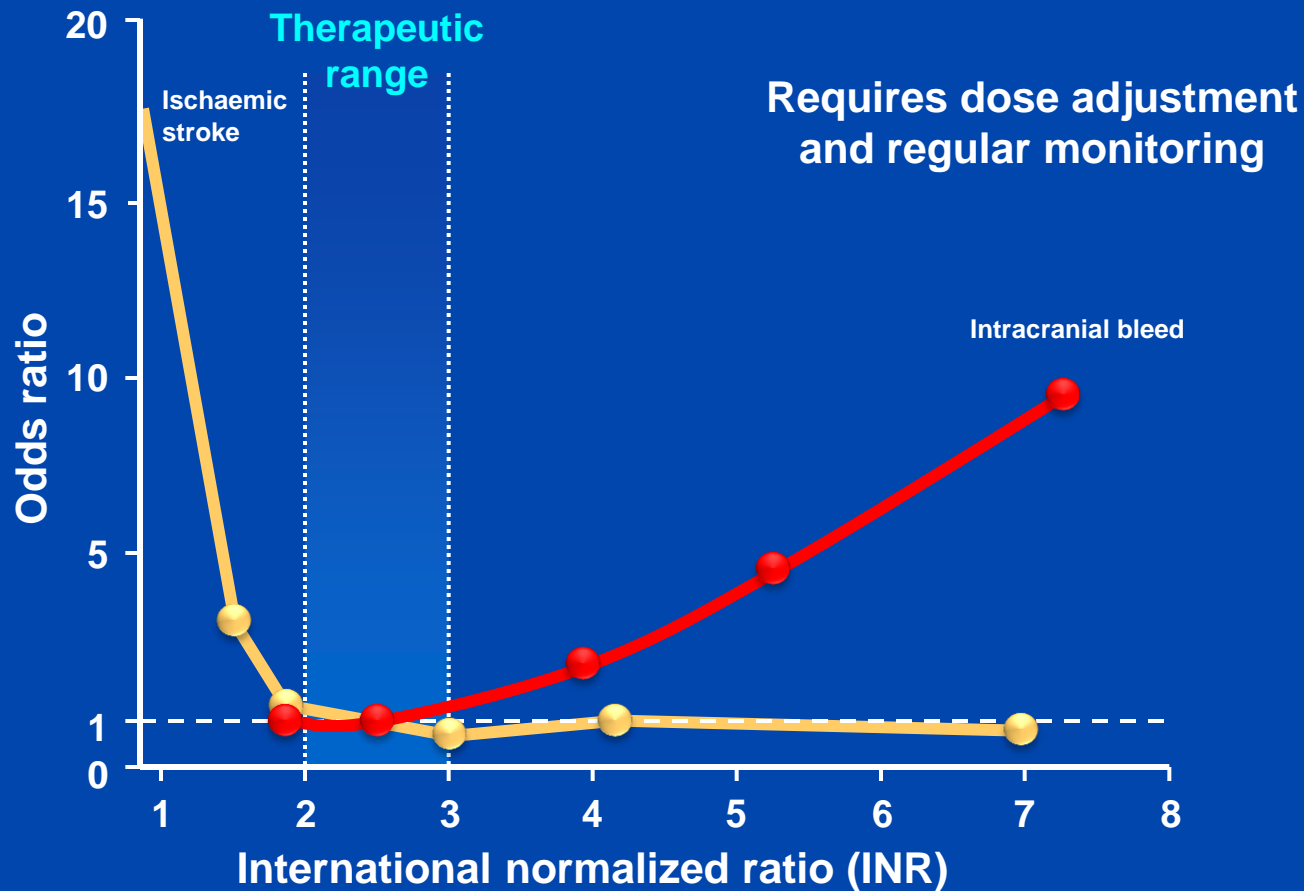
- Identify first – those at *very low stroke risk* – who should not receive anticoagulation
- With *anticoagulation offered to the remainder* taking into account bleeding risk
- Anticoagulation may be with :

- A vitamin K antagonist – **Warfarin**
- A non-vitamin K antagonist:
 - **Rivaroxaban ▼**
 - **Apixaban ▼**
 - **Dabigatran ▼**
 - **Edoxaban ▼**

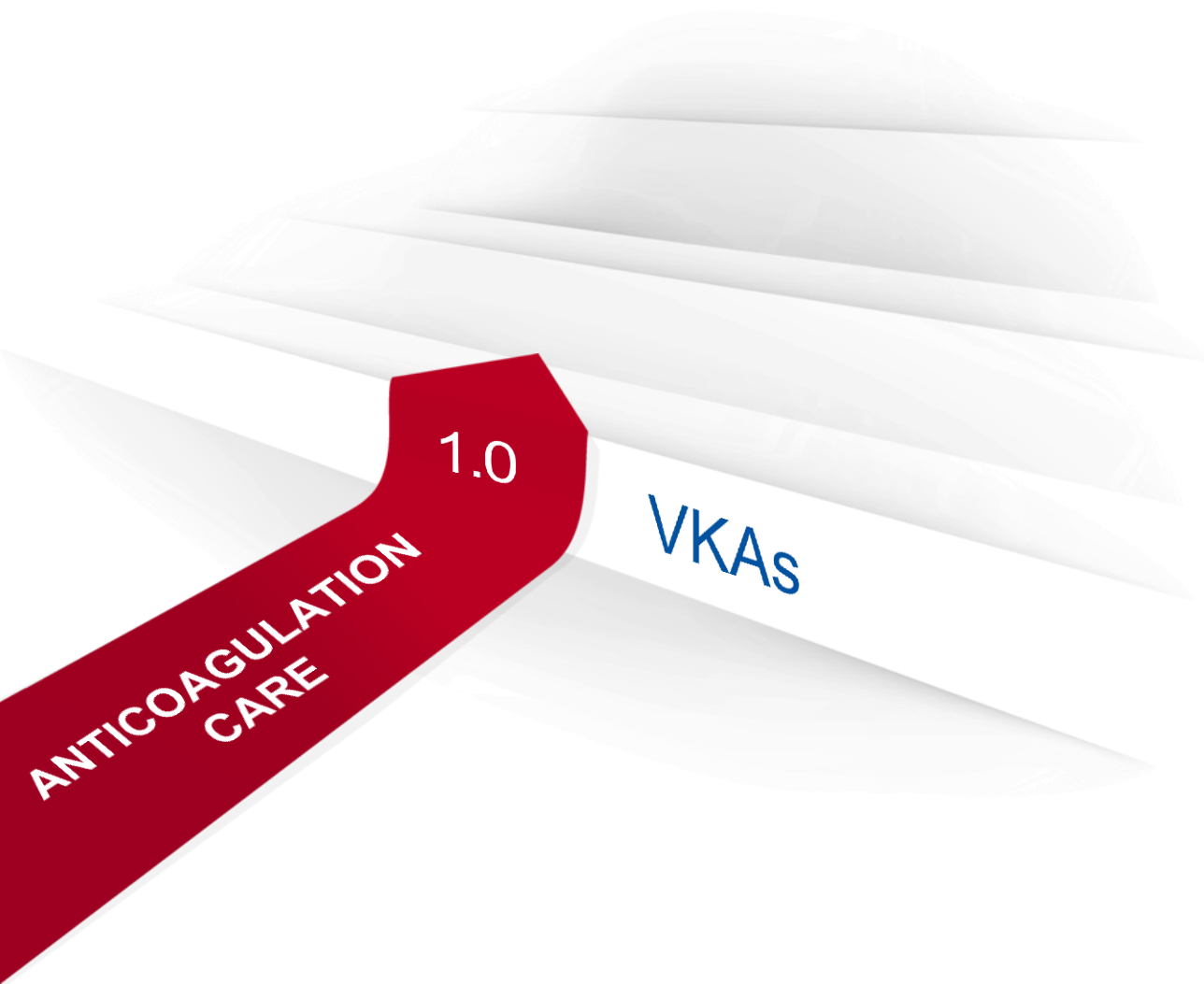


"Hold it, I wonder if I might try the warfarin again?"

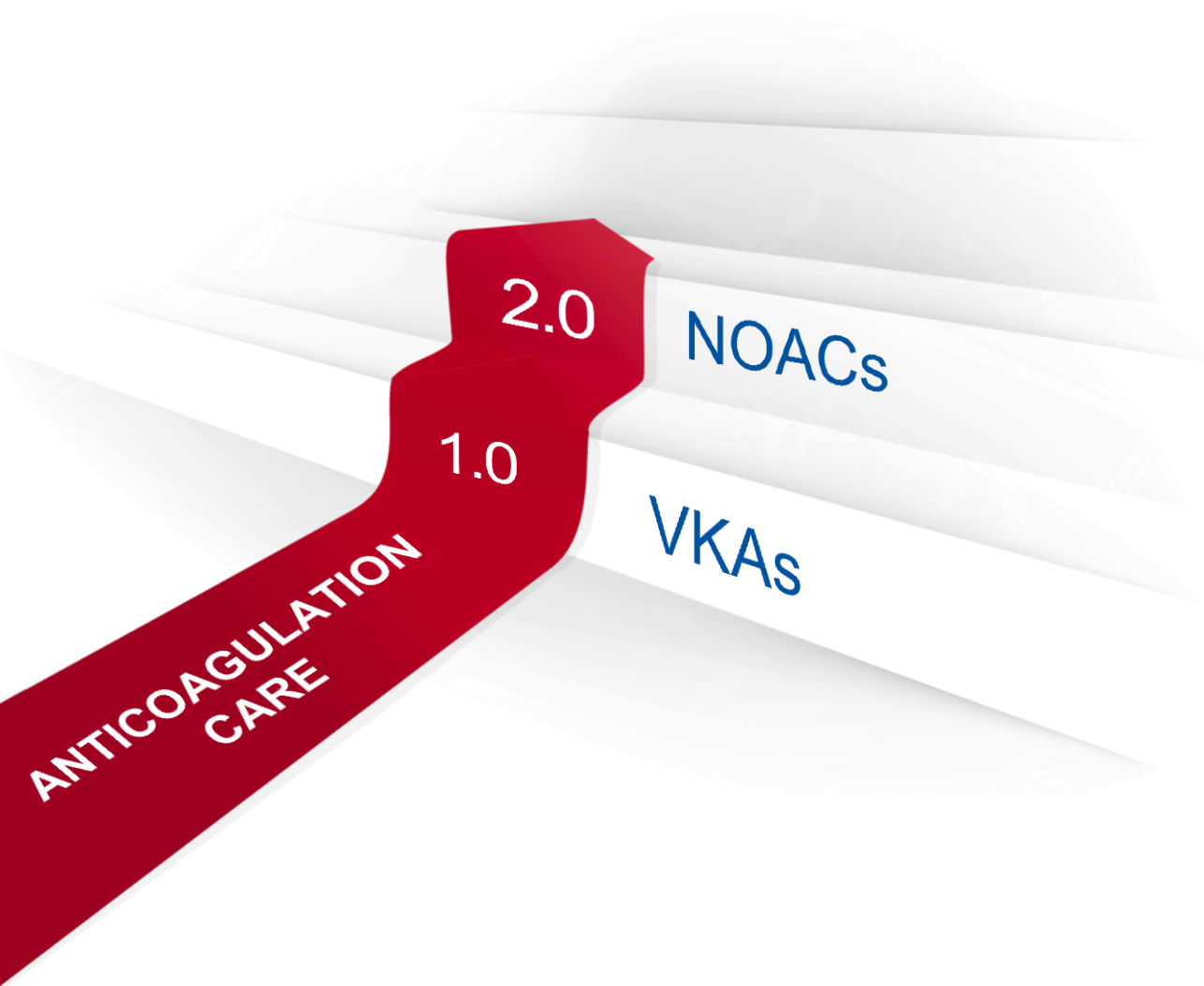
Warfarin and its challenging therapeutic window



The first oral anticoagulant

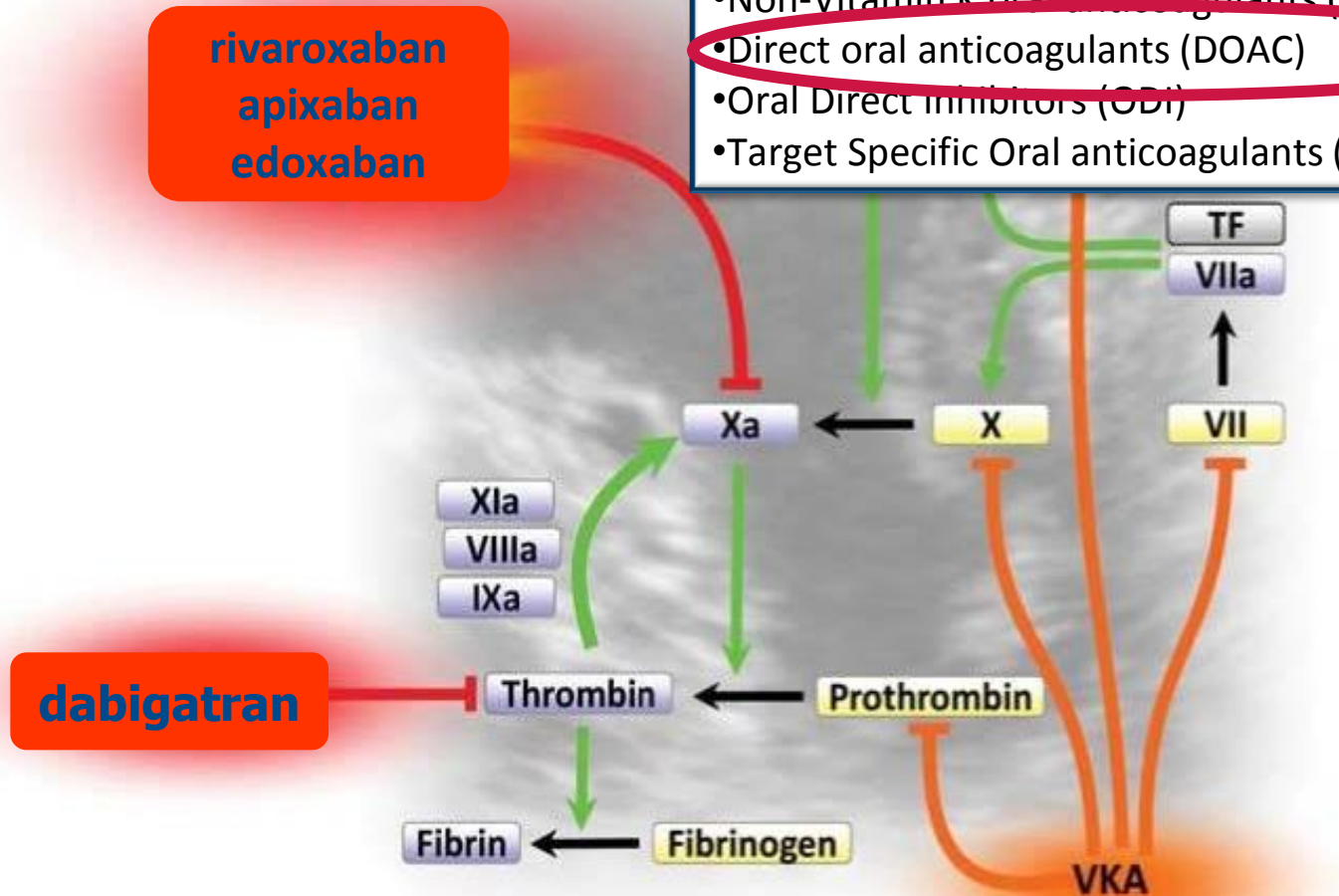


A new standard in oral anticoagulant therapy



The Novel (Direct) OACs

- Terminology.....
- New oral anticoagulants (NOAC)
- Novel Oral anticoagulants (NOAC)
- Non-Vitamin K oral anticoagulants (NOAC)
- Direct oral anticoagulants (DOAC)
- Oral Direct inhibitors (ODI)
- Target Specific Oral anticoagulants (TSOAC)



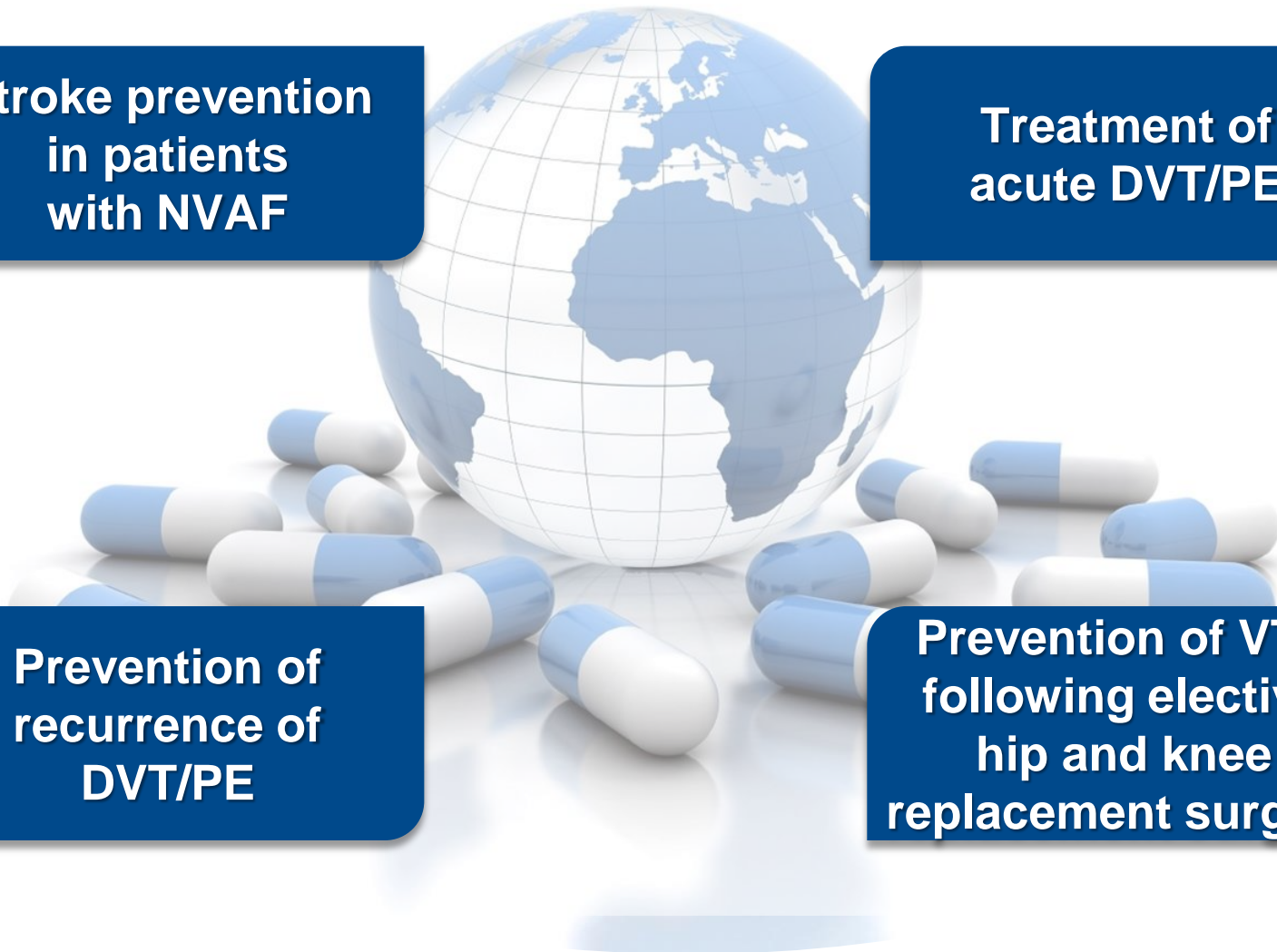
NOACs are becoming a standard therapy in multiple settings worldwide, including:

**Stroke prevention
in patients
with NVAf**

**Treatment of
acute DVT/PE**

**Prevention of
recurrence of
DVT/PE**

**Prevention of VTE
following elective
hip and knee
replacement surgery**



Novel oral anticoagulants (NOACs) : NICE recommended

Licensing	Apixaban	Edoxaban	Dabigatran	Rivaroxaban
Primary prevention of VTE in adults undergoing elective total hip and knee replacement	TA245 Jan 2012	No EU License Licensed in Japan April 2011	TA157 September 2008	TA170 April 2009
Prevention of stroke or systemic embolisation in patients with non-valvular AF	TA275 Feb 2013	TA355 Sept 2015	TA249 March 2012	TA256 May 2012
DVT treatment	TA341 June 2015	TA345 Aug 2015	TA327 Dec 2014	TA261 July 2012
PE treatment	TA341 June 2015	TA345 Aug 2015	TA327 Dec 2014	TA287 June 2013
Prevention of atherothrombotic events after an ACS	No License	No License	No License	TA335 March 2015

1. Pradaxa Summary of Product Characteristics; 2. Xarelto Summary of Product Characteristics; 3. Eliquis Summary of Product Characteristics; 4. Lixiana Summary of Product Characteristics. Current versions of SPCs available online at: <http://www.medicines.org.uk/emc/>; 5. Eriksson BI et al. Ann Rev Med 2011;62:41-57

Pharmacology

	Dabigatran ¹	Rivaroxaban ²	Apixaban ³	Edoxaban ⁴
Mode of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Half life	12-14 hours	5-9 hours (young) 11-13 hours (elderly)	12 hours	10-14 hours
Dosing	BD	OD	BD	OD
Metabolism	P-glycoprotein	CYP P450/P-glycoprotein	CYP P450/P-glycoprotein	CYP P450/P-glycoprotein
Excretion	80% Renal	33% Renal	27% Renal	50% Renal
Form	Hard capsule	Tablet	Tablet	Tablet

BD = twice daily; OD = once daily

1. Pradaxa Summary of Product Characteristics; **2.** Xarelto Summary of Product Characteristics; **3.** Eliquis Summary of Product Characteristics; **4.** Lixiana Summary of Product Characteristics. Current versions of SPCs available online at: <http://www.medicines.org.uk/emc/>

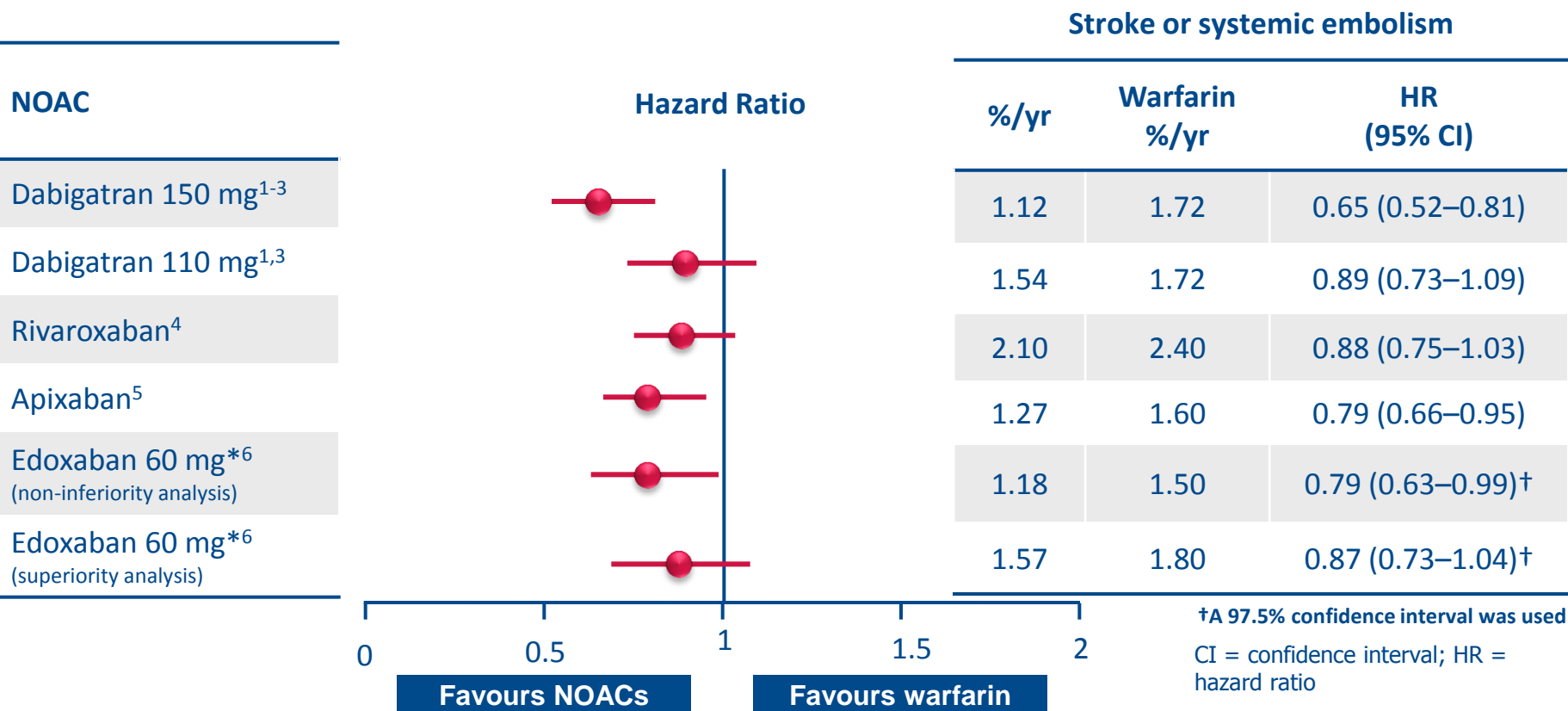
NOAC dosing regimens for Stroke prevention in AF

NOAC	Full dose	Reduced dose
Dabigatran ¹	150mg BD	110mg BD for patients aged 80 years or above or who receive concomitant verapamil. Also, for the following groups based on individual assessment of thromboembolic risk and risk of bleeding: <ul style="list-style-type: none"> •Patients aged 75-80 years •Patients with moderate renal impairment •Patients with gastritis, oesophagitis or gastro-oesophageal reflux •Other patients at increased risk of bleeding
Rivaroxaban ²	20mg OD	15mg OD for patients with moderate or severe renal impairment (CrCl 15-49ml/min)
Apixaban ³	5mg BD	2.5mg BD for patients with at least 2 of the following characteristics: <ul style="list-style-type: none"> •Age ≥80 years •Body weight ≤60 kg •Serum creatinine ≥1.5mg/dL (133 μM/L) Or with severe renal impairment (CrCL 15-29ml/min)
Edoxaban ⁴	60mg OD	30mg OD for patients with one or more of the following: <ul style="list-style-type: none"> •Moderate or severe renal impairment (CrCl 15-50ml/min) •Low body weight (≤60 kg) •Concomitant use of the following P-gp inhibitors: cyclosporin, dronedarone, erythromycin or ketoconazole

1

Product Characteristics. Current versions of SPCs available online at: <http://www.medicines.org.uk/emc/>

NOAC trial outcomes: Stroke and systemic embolism vs warfarin

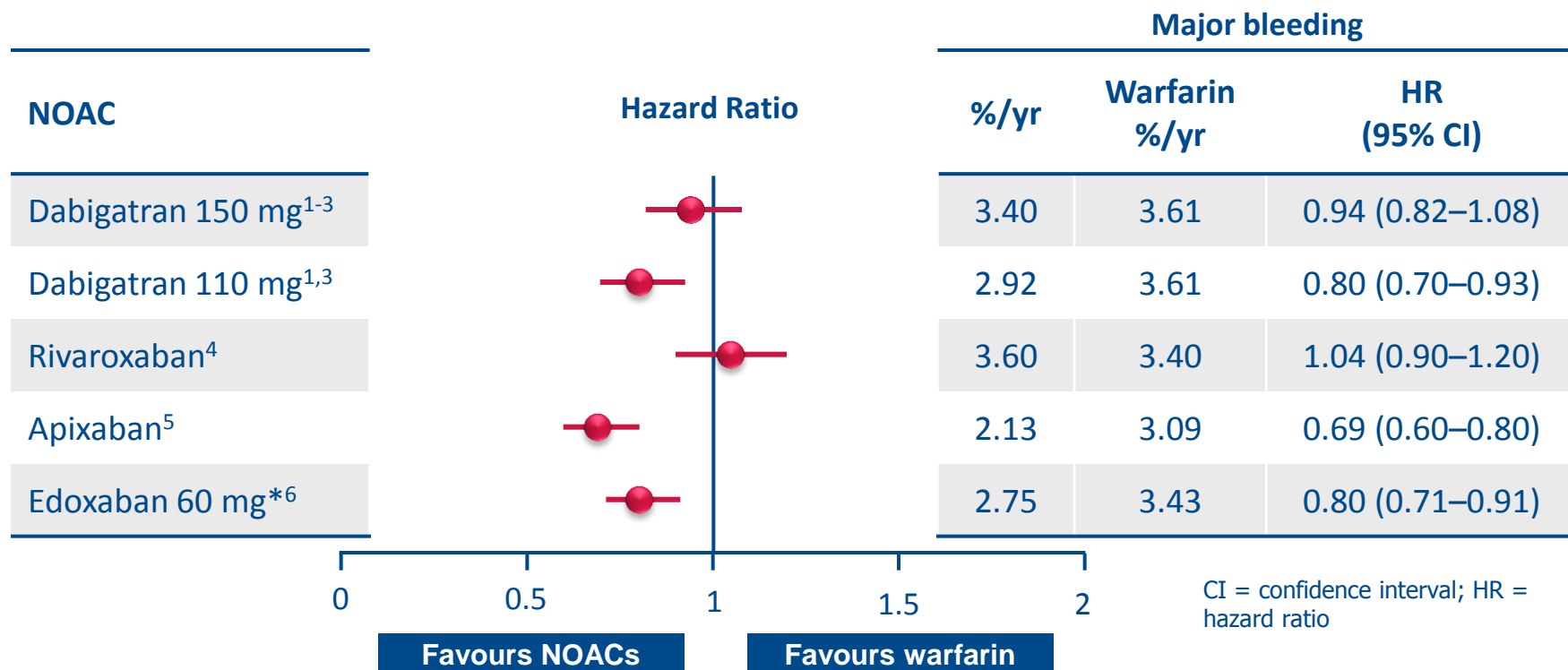


*There was a dose reduction to 30mg in the 60mg arm; 30mg arm data are not shown as this is not a licensed dosing regimen.
Non-Inferiority – Modified intention-to-treat population in the treatment period. Superiority – Intention-to-treat population in the overall study period.

Clinical trial data for information only - no clinical conclusions should be drawn. Please refer to individual product SPCs for further information. Analyses were performed on data from the intention-to-treat population

1. Connolly SJ et al. N Engl J Med. 2009;361:1139–51; **2.** Connolly SJ et al. N Engl J Med. 2010; 363:1875-6; **3.** Connolly SJ et al. N Engl J Med. 2014;371:1464–5; **4.** Patel MR et al. NEJM. 2011;365:883–91; **5.** Granger et al. N Eng J Med 2011;365:981-92; **6.** Giugliano et al. N Engl J. 2013;369:2093–104.

NOAC trial outcomes: Major bleeding versus warfarin

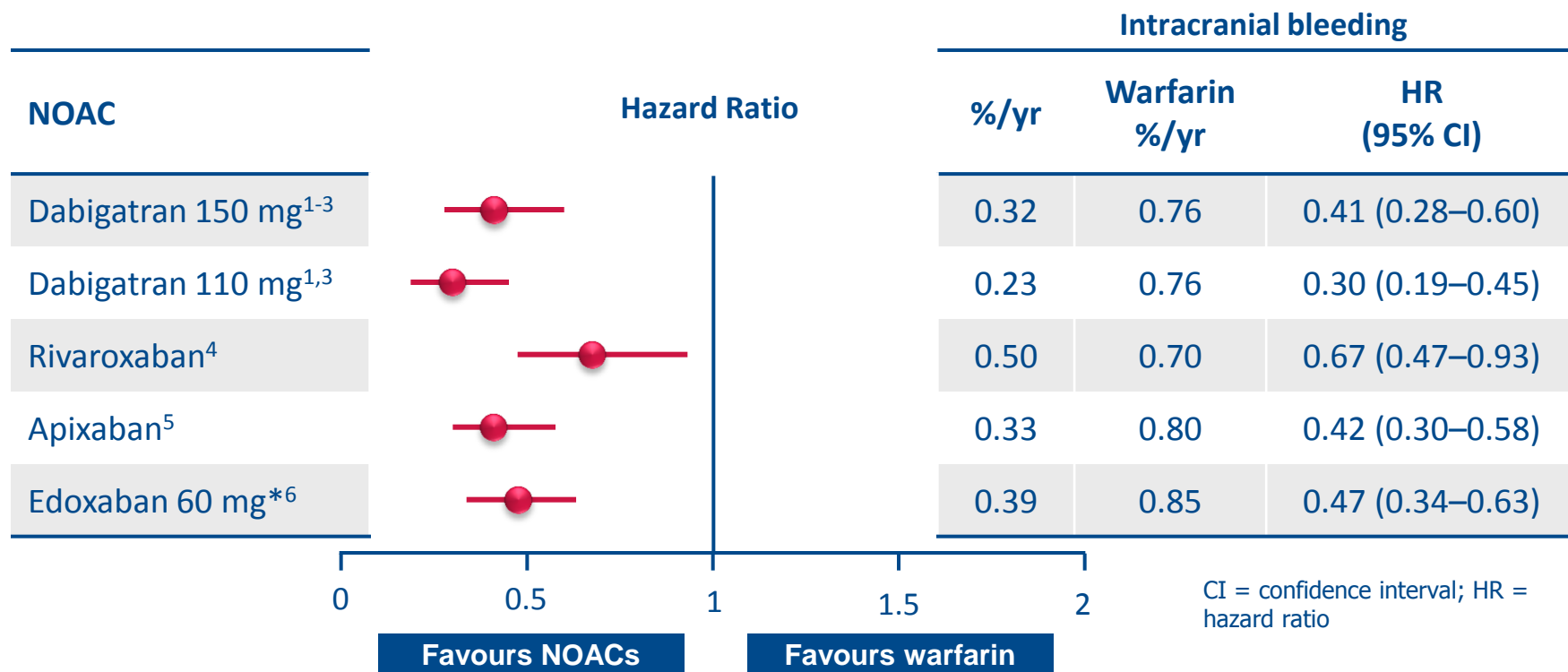


*There was a dose reduction to 30mg in the 60mg arm; 30mg arm data are not shown as this is not a licensed dosing regimen.

Clinical Trial Data for information only - no clinical conclusions should be drawn. Please refer to individual product SPCs for further information.

1. Connolly SJ et al. N Engl J Med. 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med. 2010; 363:1875-6; 3. Connolly SJ et al. N Engl J Med. 2014;371:1464–5; 4. Patel MR et al. NEJM. 2011;365:883–91; 5. Granger et al. N Eng J Med 2011;365:981-92; 6. Giugliano et al. N Engl J. 2013;369:2093–104.

NOAC trial outcomes: Intracranial bleeding vs warfarin

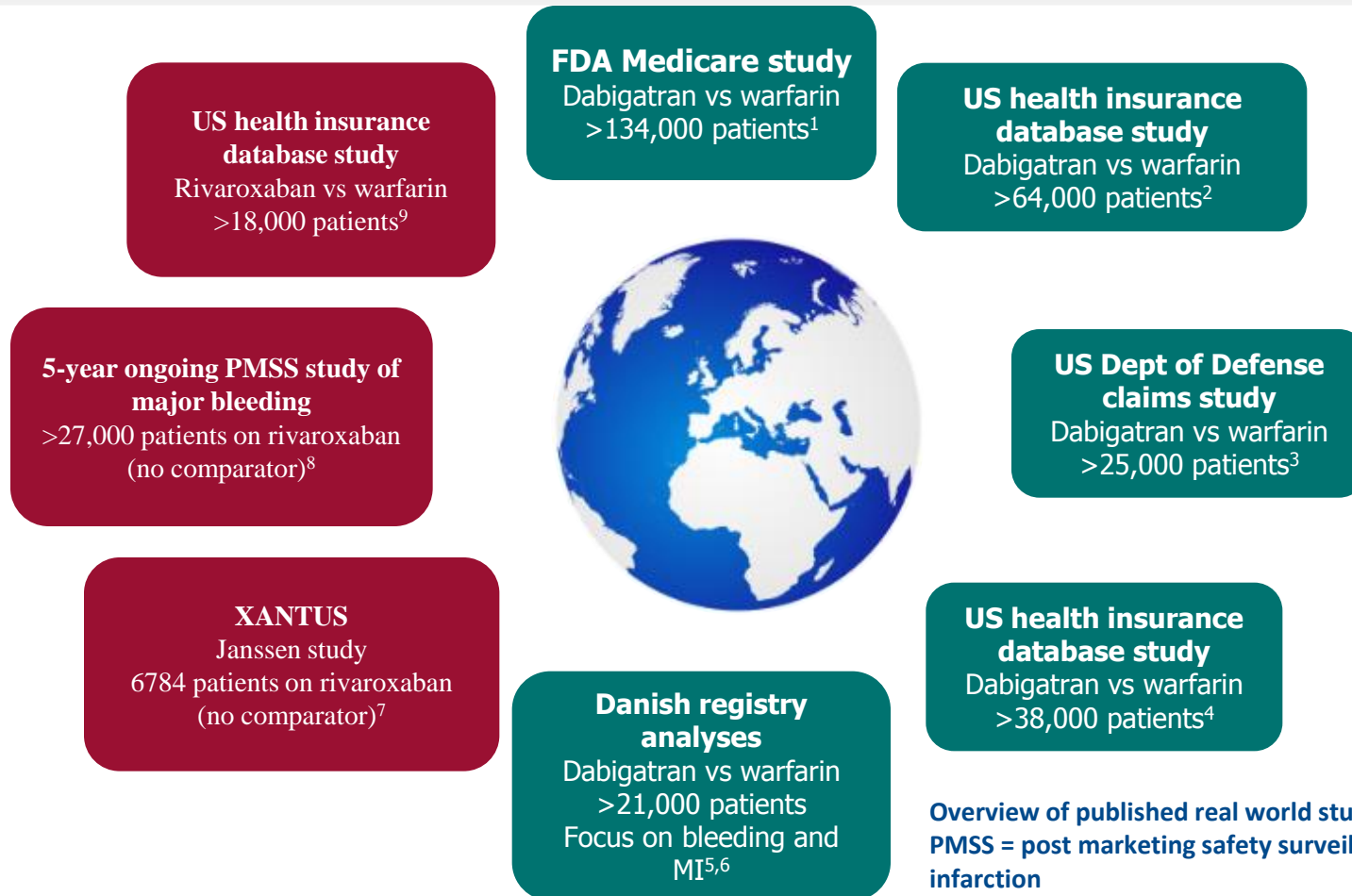


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1. Connolly SJ et al. N Engl J Med. 2009;361:1139–51; 2. Connolly SJ et al. N Engl J Med. 2010; 363:1875-6; 3. Connolly SJ et al. N Engl J Med. 2014;371:1464–5; 4. Patel MR et al. NEJM. 2011;365:883–91; 5. Granger et al. N Engl J Med 2011;365:981-92; 6. Giugliano et al. N Engl J. 2013;369:2093–104.

Real world evidence for NOACs in patients with AF is increasingly available showing consistency with phase III trials



Overview of published real world studies – list not exhaustive
PMSS = post marketing safety surveillance; MI = myocardial infarction

1. Graham DJ et al. Circulation 2015;131:157-64; 2. Lauffenburger JC et al. J Am Heart Assoc 2015;4:e001798; 3. Villines TC et al. Thromb Haemost 2016;115 epub ahead of print; 4. Seeger JD et al Thromb Haemost 2016;115 epub ahead of print; 5. Larsen TB et al. Am J Med 2014;127:329–36; 6. Larsen TB et al. Am J Med 2014;127:650–6; 7. Camm J et al. Eur Heart J 2015 epub ahead of print; 8. Tamayo S et al. Clin Cardiol 2015;38(2):63-68; 9. Laliberte F et al. Curr Med Res Opin 2014;30(7):1317-1325.

UK National Institute for Health and Care Excellence (NICE)

NOACs must be made available for prescribing within their licensed indications, and should be automatically included in local formularies¹

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation ²

Technology appraisal guidance
Published: 15 March 2012
[nice.org.uk/guidance/ta249](https://www.nice.org.uk/guidance/ta249)

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation ³

Technology appraisal guidance
Published: 23 May 2012
[nice.org.uk/guidance/ta256](https://www.nice.org.uk/guidance/ta256)

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation ⁴

Technology appraisal guidance
Published: 27 February 2013
[nice.org.uk/guidance/ta275](https://www.nice.org.uk/guidance/ta275)

Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation ⁵

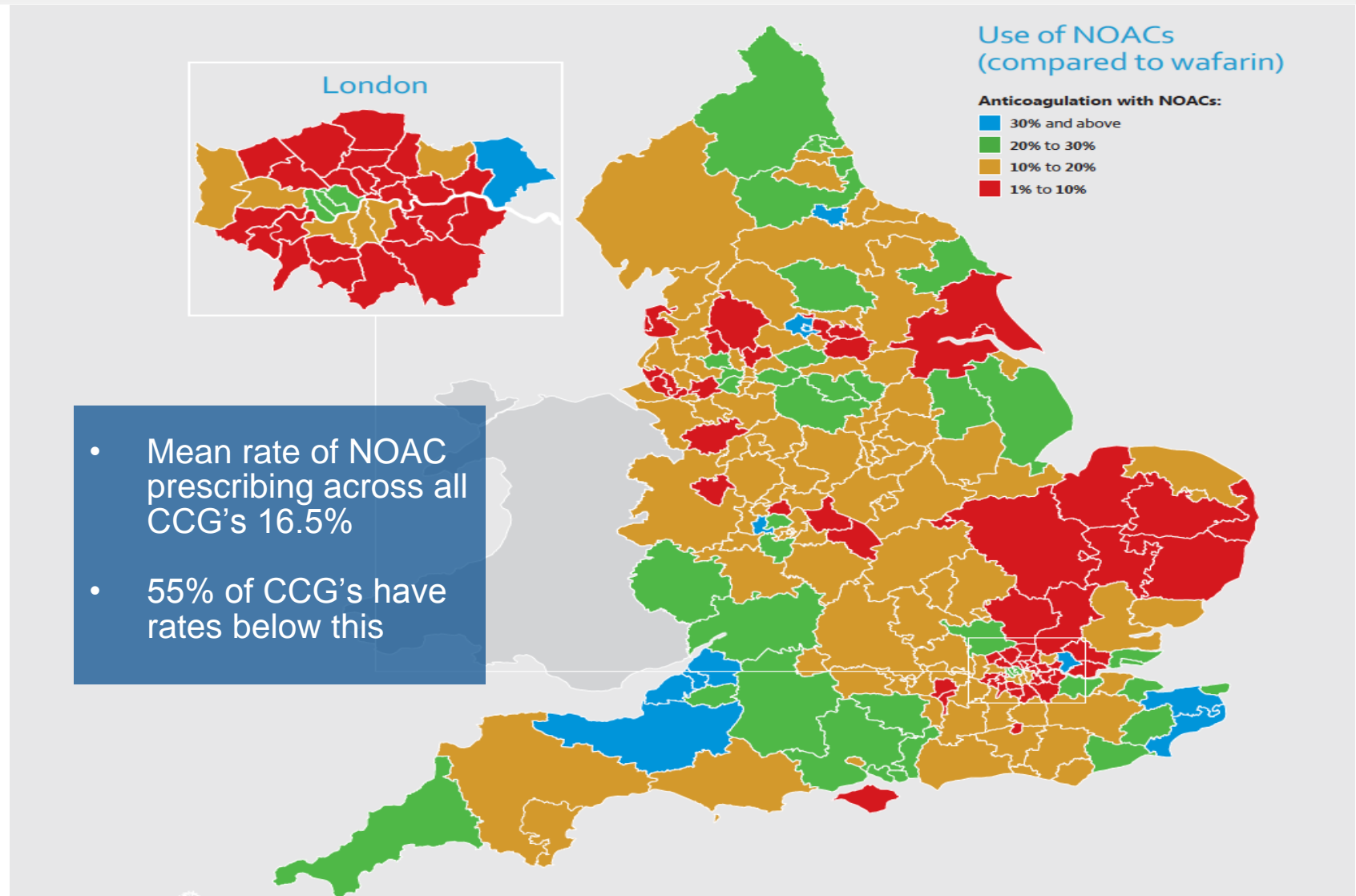
Technology appraisal guidance
Published: 23 September 2015
[nice.org.uk/guidance/ta355](https://www.nice.org.uk/guidance/ta355)

1. NICE consensus statement on the use of NOACs. Available at:

<https://www.nice.org.uk/guidance/cg180/resources/nic-consensus-statement-on-the-use-of-noacs-243733501>;

2. NICE TA249, 2012; 3. NICE TA256, 2012; 4. NICE TA275, 2013; 5. NICE TA355, 2015

NOAC uptake in England (NHS data)



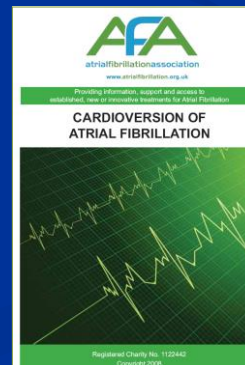
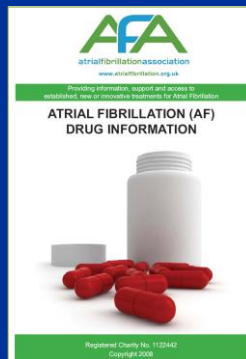
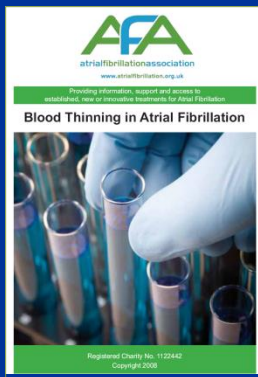
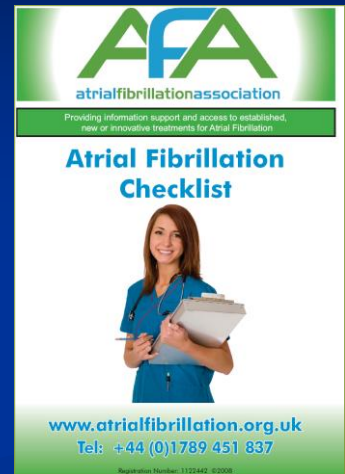
Review of stroke and anticoagulation risk

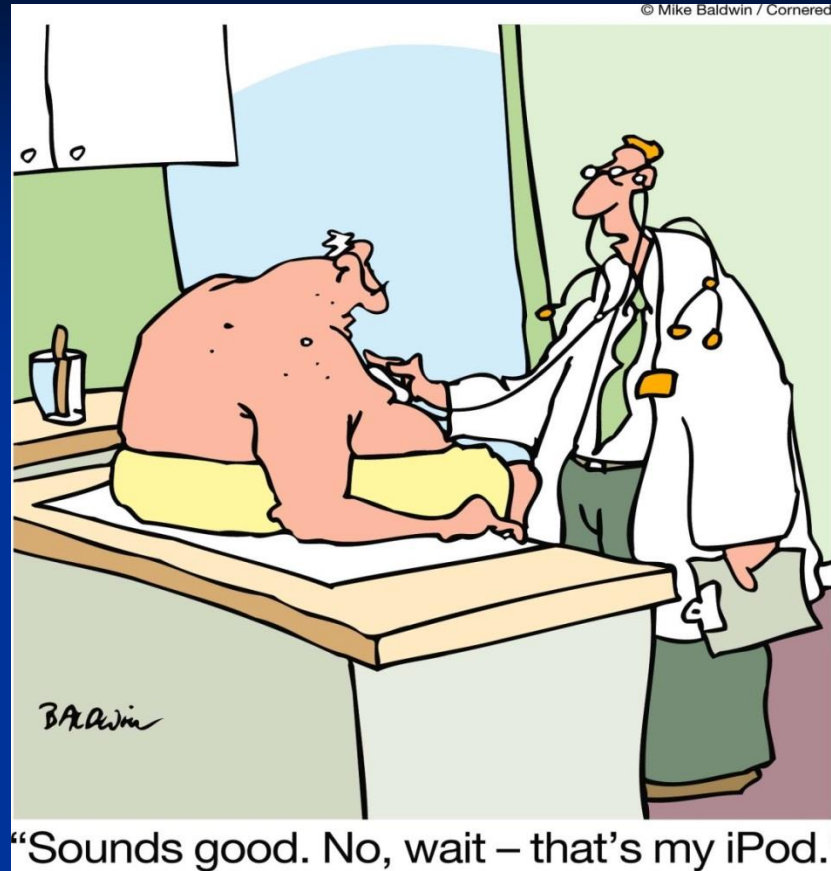
- All people with atrial fibrillation should undergo review at least annually
- For people not taking an anticoagulant, review stroke risk when they reach age 65 or *develop any of the following* at any age:

- Diabetes
- Heart failure
- Coronary artery disease
- TIA or stroke
- Peripheral vascular disease

Patient support

- Information booklets
- Fact Sheets
- Website: www.atrialfibrillation.org.uk
- Email: info@atrial-fibrillation.org.uk
- 24/7 Helpline: 01789 451 837





Thank-you...any questions?

Preventing stroke in West Hampshire

We want to: improve the identification of asymptomatic/undiagnosed AF in WHCCG (an estimated 2000 patients) via opportunistic screening utilising the NICE endorsed WatchBP monitor; saving target - 30 strokes per year at a cost of £126k with zero investment.

National drivers



NICE National Institute for Health and Care Excellence

WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension

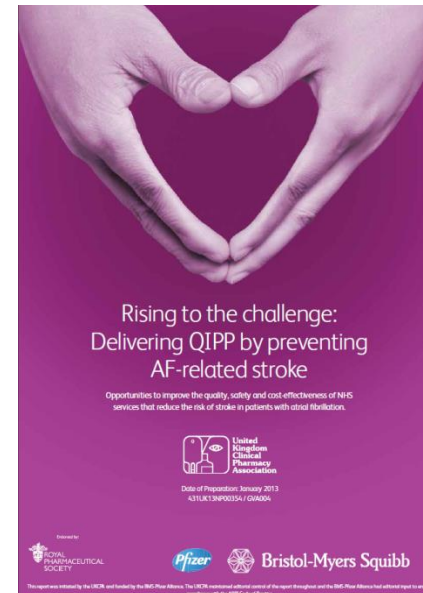
Issued: January 2013

NICE medical technology guidance 13
guidance.nice.org.uk/mtg13

This is an extract from the guidance. The complete guidance is available at guidance.nice.org.uk/mtg13

NICE has accredited the process used by the Centre for Health Technology Evaluation at NICE to produce medical technologies guidance. Accreditation is valid for 5 years from November 2011 and applies to guidance produced since March 2011 using the processes described in NICE's Medical Technologies Evaluation Programme: methods guide (2011) and Medical Technologies Evaluation Programme: process guide (2011). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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Preventing stroke in West Hampshire – Strategy

A collaborative plan involving WHCCG Long Term Conditions/GPs/Medicines management and pharmacy

STEP 1

PROACTIVE LEADERSHIP

- Awareness raising/Public Health Audit 2012
- Multi-level educational sessions/events
- Use of incentives/levers QOF/LES/QIPP
- Analysis/needs-gap evaluation/business case

STEP 2

OPPORTUNISTIC SCREENING

- Screening programme targeting high risk asymptomatic patients
- Introduction of NICE endorsed WatchBPTool
- Early adopter 3B Practices/wider roll-out WHCCG
- Reinforce educational sessions

STEP 3

OPTIMISING ANTICOAGULATION AND REPORTING

- Medicines Management LES – Quality/Safety Intervention
- Anticoagulation education – NOACS v Warfarin
- Improving uptake of GRASP – AF Tool + WPSAT/CHADS2VASC
- Uploading to National dataset
- Community Pharmacy Interventions
- NICE KPIs

STEP 4

EVALUATION/AUDIT

- Record monitor progress improvements via GRASP – AF
- Increased NOAC prescribing audit
- Introduction of AF/anticoagulation nurse?
- Public Health Audit/participation in National trials Oxford + Southampton
- Review of anticoagulation provision/increasing INR self- testing opportunities/primary care community delivered cardiology services