Transient Ischaemic Attack

Prof Ganesh Subramanian
Stroke Consultant

This promotional meeting is organised and funded by Pfizer Ltd

on behalf of the Bristol-Myers Squibb – Pfizer Alliance

Prescribing Information for **Eliquis (apixaban**) licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke or transient ischaemic attack; age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II) is available at this meeting or attached to the Joining Instructions if joining via WebEx.

Adverse events should be reported. Reporting forms and information can be found at: UK - www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Bristol-Myers Squibb via medical.information@bms.com or 0800 731 1736 (UK)

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Prescribing information for **Eliquis® (apixaban**) licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, with one or more risk factors, such as prior stroke or transient ischaemic attack; age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II) is available at this meeting on request

PP-ELI-GBR-6448 March 2020

Objectives

- TIA – what it is and what it's not
- Assessment and investigations
- Management

Transient Ischaemic Attack

- Acute episode of focal loss of cerebral or visual function lasting less than 24 hrs, and attributable to inadequate blood supply.
- Most last for < 1 hour

- ASA – Transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without evidence of acute infarction

Diagnostic challenges

- Event occurred in the past, often unwitnessed
- Reliant on patient's history
- -Pt may be unable to completely recall symptoms
- -May use vague descriptions "dizziness", "confused", "heaviness"
- Clinical examination usually normal
- Many causes of transient neurology (50% of pts referred to TIA clinic)
- No diagnostic test

TIA-a vascular event

- Focal symptoms
- Negative symptoms
- Sudden onset
- Max at onset

Non focal symptoms

- Faintness/lightheadedness
- Confusion
- Syncope
- Non specific dizziness
- Incontinence
- Vertigo

Transient Focal Neurology

- TIA
- Focal epilepsy
- Migraine aura (+/- headache)
- Transient Global Amnesia
- Multiple sclerosis
- Intracranial structural lesion
- Metabolic disturbance
- Psychological

Case 1 - 50 year old female

- Heaviness and pins and needles in (L) hand
- Gradually spread to (L) arm and face
- Distortion of vision (L) visual field
- Resolved within 30 minutes.
- No past medical history

Migraine aura +/- headache

- 25% of migraine pts have aura – precedes headache

- Visual symptoms common
  - Photopsia (flashes of light)
  - Teichopsia (fortification spectrum)
  - Distortion of vision
  - Scotoma

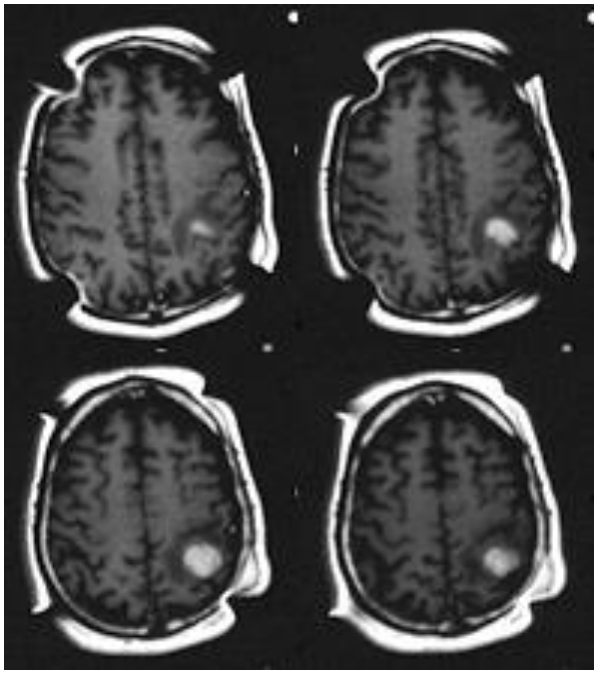
- Usually last 15-30 minutes

Migraine aura +/- headache

- Neurological symptoms
- Paraesthesia, tingling most common-**spreads** up or down limbs- "march" of symptoms
- Speech disturbance
- Mild weakness (rare)
- 10-30 minutes
- Area where symptoms started resolves first
- Headache may be absent in older people
- Migraine with aura - ↑ stroke risk

Case 2 - 64 year old male

- Recurrent episodes of pins and needles in (R) arm and leg over past 4 weeks.
- Sensation started in (R) foot and quickly spread to involve whole arm and leg.
- Each episode lasted 5 minutes.
- Episodes were identical.



- MRI – (L) parietal glioblastoma

Focal seizures

- Can cause transient neurological symptoms
- Symptoms start abruptly
- Symptoms spread quickly (more rapidly than migraine)
- Positive symptoms – jerking, tingling

Case 3 - 72 year old male

- At the gym, drove home
- According to wife –"confused", repeatedly asking "What day is it?"
- No limb or facial weakness
- Symptoms resolved after 4 hours
- Pt has no recollection of event

Transient Global Amnesia

- Temporary, isolated disorder of memory
- Impaired ability to form new memory
- Asks pertinent questions repeatedly

- Preservation of language, attention, visuo-spatial and social skills

- Symptoms last < 24 hours

- Unable to recall episode once recovered

- Precise pathophysiology unclear

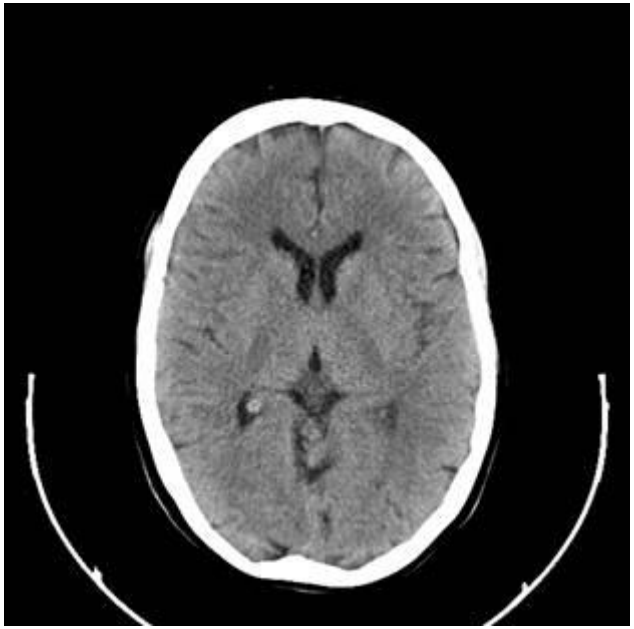
Transient Global Amnesia

- 3/100,000 cases per annum
- More common in males
- Precipitants – physical exertion, cold water exposure, overwhelming emotional stress, pain
- Annual recurrence rate 3%
- No increased risk of stroke

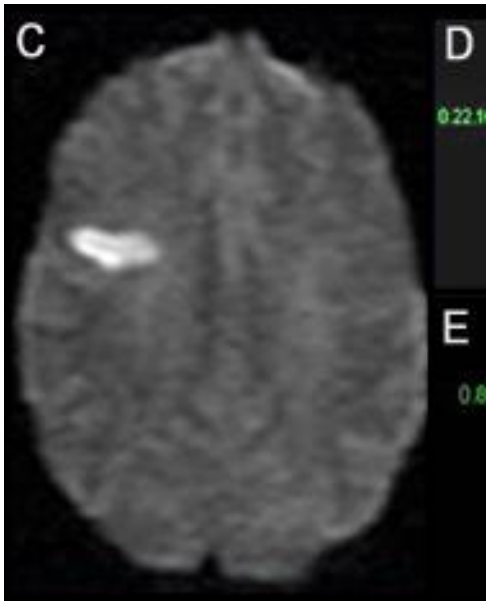
Case 4 – 27 year old male

- Sudden onset numbness and weakness in (L) hand
- Resolved within 1 hour
- No past medical history

CT head



MRI-DWI



What's the urgency?

- Common

- Serious recurrent vascular events
- Stroke, MI, death

- Most occur in first few days
- 5% stroke within 2 days
- 11% stroke within 1 week

EXPRESS Trial

- 90 day risk of recurrent stroke
- Phase 1 – 10.3%
- Phase 2 – 2.1%

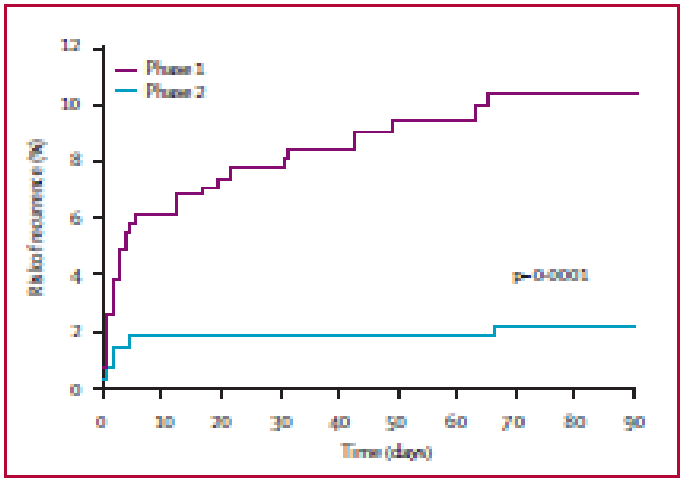


Figure 2: Risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke who were referred to the study clinic

- Independent of age and sex
- No increase in risk of intracerebral haemorrhage or other bleeding

Rothwell et al. Lancet 2007;370:1432-1442

ABCD2 Score

- Age > 60yrs = 1 point
- Blood pressure >140/90 = 1 point
- Clinical features
  - Unilateral weakness = 2 points
  - Speech disturbance only = 1 point
- Duration of symptoms
  - > 60min = 2 points
  - 10 – 59min = 1 point
- Diabetes = 1 point

Risk stratification

ABCD2 Score	2 day risk	7 day risk
0-3	1.0%	1.2%
4-5	4.1%	5.9%
6-7	8.1%	11.7%

Johnston, Rothwell et al. Lancet 2007;369:283-292

ABCD2 Score

- Does not reliably discriminate between low/high risk of recurrent stroke, or those with Carotid Stenosis or AF
- Sensitive but not specific
- 35% mimics and 66% of true TIAs had score ≥ 4
- 20% of score < 4 had AF or Carotid Stenosis

Wardlaw et al, Neurology 2015

All TIAs must be assessed and treated within 24 hours!

RCP guidelines 2016

Specialist Assessment

- Confirm the diagnosis of TIA and its vascular territory
- Arrange appropriate investigations
- Assessment and management of vascular risk factors

Risk Factors

- Hypertension
- Atrial fibrillation
- Diabetes Mellitus
- Previous TIA/CVA
- Ischaemic heart disease
- Alcohol
- Peripheral vascular disease
- Cigarette smoking
- Hyperlipidaemia
- Age
- Family history

Brain Imaging

- Indicated if underlying pathology or vascular territory is uncertain

- Should be performed within 24 hours of symptom onset

- MRI-DWI imaging modality of choice
- CT if MRI unavailable

NICE Guidelines 2008

Secondary Prevention

- Antiplatelets

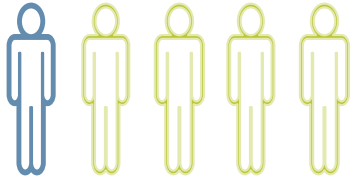
  Single antiplatelet vs. dual antiplatelets for 3 weeks

- Lipid lowering (Cholesterol >4)

- Antihypertensives (BP<130/80mmHg)

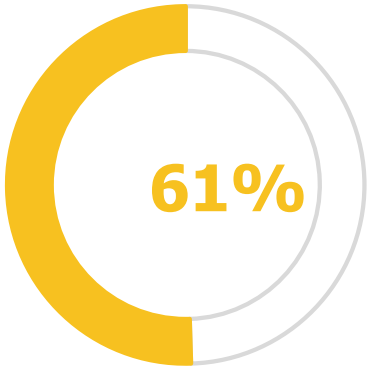
Stroke patients with known AF: The facts

The Sentinel Stroke National Audit Programme* (April 2018–March 2019) revealed:[1]



1 in 5

stroke patients had known AF (n=16,761/87,632)



of stroke patients with known AF were anticoagulated (n=10,266/16,761)

>4,600

patients with AF-related stroke were not anticoagulated without clear justification[†]

* Includes data for England, Wales and Northern Ireland; † An additional 1,923 patients had justifiable reasons not to be anticoagulated.
AF, atrial fibrillation

1. The Sentinel Stroke National Audit Programme (SSNAP) Annual Results Portfolio April 2018-March 2019. Available at: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx (last accessed December 2019).

How do you detect A fib?

- 12 lead ECG
- Single lead screening
- Apple watch?
- 24 hr tape
- Prolonged monitoring (7 day tape or ILR)

How can the risk of disabling stroke be reduced?

- Study end points – stroke and/or systemic embolism

- Aspirin
  - Pooled analysis of 3 RCTs
    - Aspirin vs Placebo, relative risk reduction of 21% (95% CI 0% - 38%)

- Warfarin
  - Pooled analysis of 6 RCTs
    - Warfarin vs Placebo, relative risk reduction of 62% (95% CI 48% - 72%)
  - Pooled analysis of 5 RCTs
    - Warfarin vs Aspirin, relative risk reduction of 36% (95% CI 14% - 52%)
  - Older patients – BAFTA study (age ≥ 75 yrs)
    - Warfarin vs Aspirin, relative risk reduction of 53%

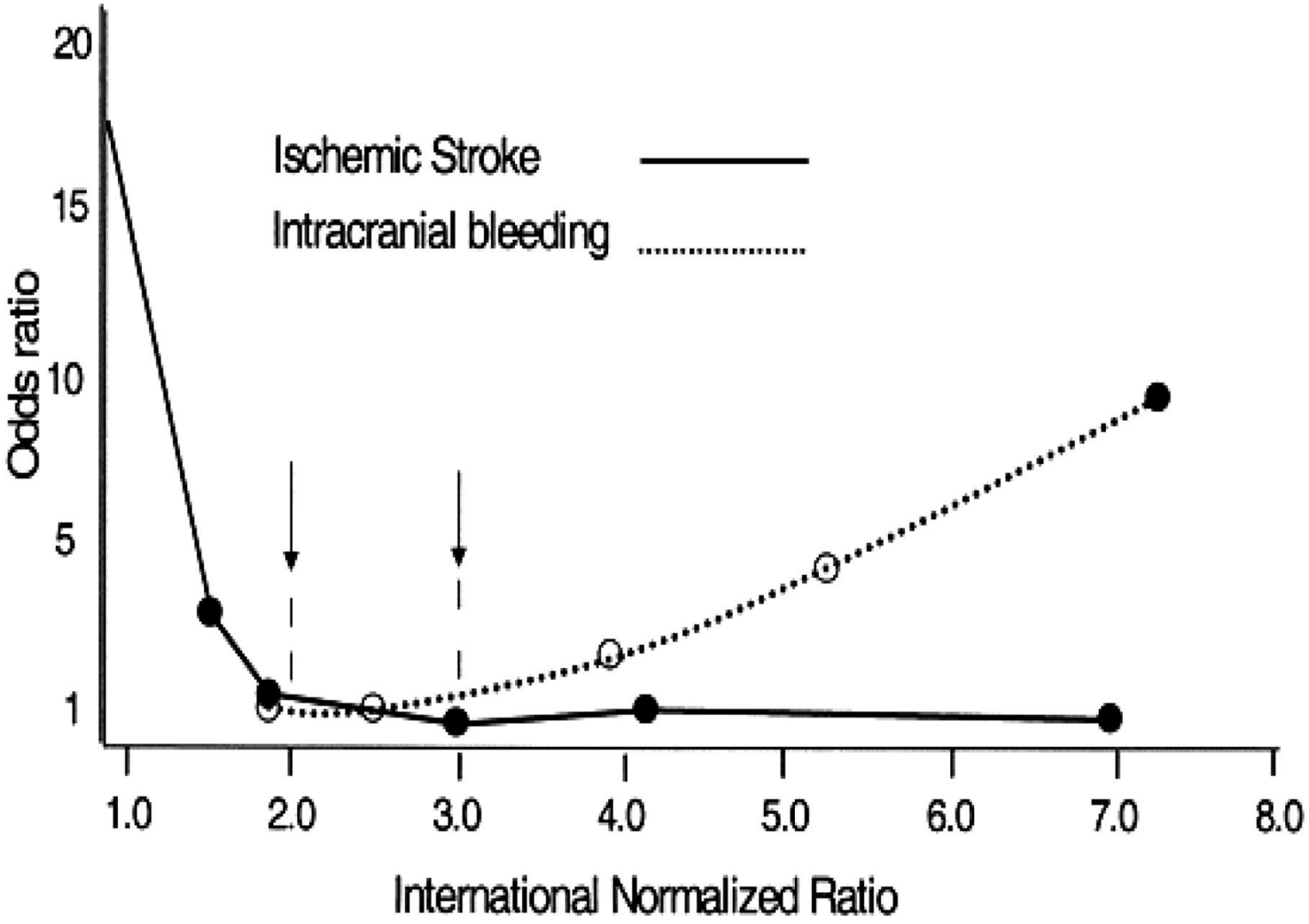
Cochrane Database Syst Rev. 2007; (3):CD006186,
BAFTA trial, Lancet. 2007;370:493-503

How good is warfarin?

- NNT for primary prevention 32

- NNT for secondary prevention 12.5

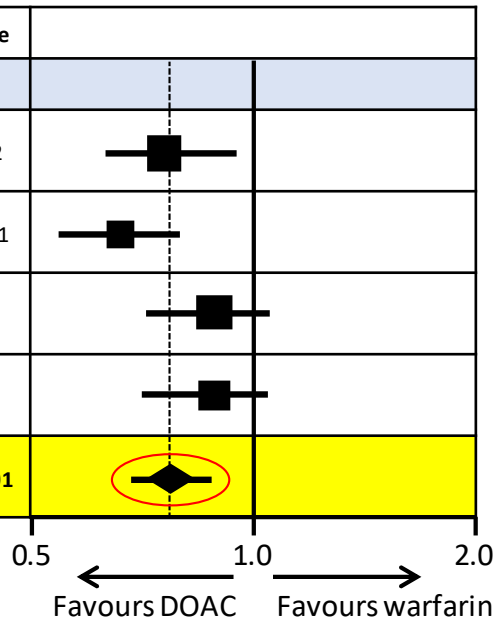
Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation



Fuster V et al. Circulation 2006;114:700-752

Meta-analysis: pooled data of DOACs vs warfarin for stroke prevention in patients with NVAF: Stroke or SE events[1]

	Events		RR (95% CI)	*P* value
Study	**DOAC, n/N (%)**	**Warfarin, n/N (%)**		
ARISTOTLE (apixaban)*	212/9,120 (2.32)	265/9,081 (2.92)	0.80 (0.67–0.95)	0.012
RE-LY (dabigatran)†‡	134/6,067 (2.21)	199/6,022 (3.30)	0.66 (0.53–0.82)	0.0001
ROCKET AF (rivaroxaban)§	269/7,081 (3.80)	306/7,090 (4.32)	0.88 (0.75–1.03)	0.12
ENGAGE AF-TIMI 48 (edoxaban)¶	296/7,035 (4.21)	337/7,036 (4.79)	0.88 (0.75–1.02)	0.10
Combined (random)	**911/29,312 (3.11)**	**1,107/29,229 (3.79)**	**0.81 (0.73–0.91)**	**<0.0001**



Heterogeneity: I^2=47%, *P*=0.13

There are no head-to-head randomised clinical trials comparing the DOACs. Comparisons cannot be made between individual DOACs based on these data.

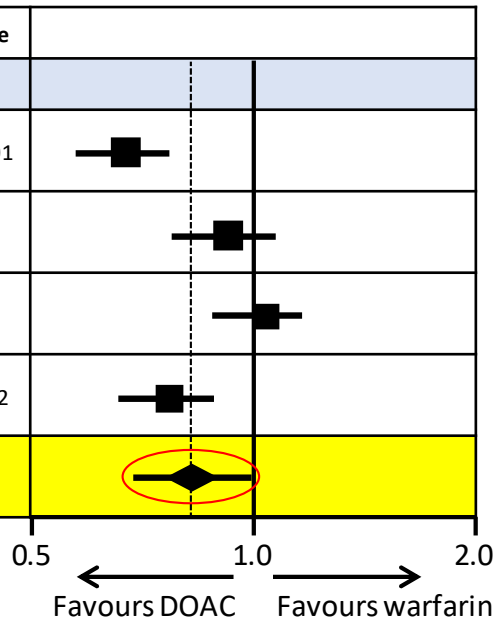
Ruff et al. 2014[1]

Analyses are based on the ITT population.
**Apixaban 5 mg BD; †Dabigatran 150 mg BD; ‡Number of events in the warfarin group of the RE-LY study has been updated to 202/6,022 since the publication of this paper; §Rivaroxaban 20 mg OD;*
¶Edoxaban 60 mg OD.
BD: twice daily; CI: confidence interval; ITT: intention-to-treat; DOAC: non-vitamin K antagonist oral anticoagulant; NVAF: non-valvular atrial fibrillation; OD: once daily; RR: risk ratio; SE: systemic embolism.

1. Ruff CT, et al. *Lancet* 2014;383:955–962.

Meta-analysis: pooled data of DOACs vs warfarin for stroke prevention in patients with NVAF: Major bleeding profiles[1]

	Events		RR (95% CI)	*P* value
Study	**DOAC, n/N (%)**	**Warfarin, n/N (%)**		
ARISTOTLE (apixaban)*	327/9,088 (3.60)	462/9,052 (5.10)	0.71 (0.61–0.81)	<0.0001
RE-LY (dabigatran)†	375/6,076 (6.17)	397/6,022 (6.59)	0.94 (0.82–1.07)	0.34
ROCKET AF (rivaroxaban)‡	395/7,111 (5.55)	386/7,125 (5.42)	1.03 (0.90–1.18)	0.72
ENGAGE AF-TIMI 48 (edoxaban)§	444/7,012 (6.33)	557/7,012 (7.94)	0.80 (0.71–0.90)	0.0002
Combined (random)	**1,541/29,287 (5.26)**	**1,802/29,211 (6.17)**	**0.86 (0.73–1.00)**	**0.06**



Heterogeneity: I^2=83%, *P*=0.001

There are no head-to-head randomised clinical trials comparing the DOACs. Comparisons cannot be made between individual DOACs based on these data.

Ruff et al. 2014[1]

Analyses are based on the safety population (patients who received at least one dose of study drug). Please refer to individual study details for further information.
**Apixaban 5 mg BD; †Dabigatran 150 mg BD; ‡Rivaroxaban 20 mg OD; §Edoxaban 60 mg OD.*
BD: twice daily; CI: confidence interval; DOAC: non-vitamin K antagonist oral anticoagulant; NVAF: non-valvular atrial fibrillation; OD: once daily; RR: risk ratio.

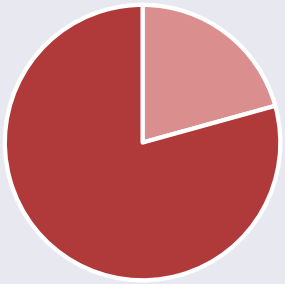
1. Ruff CT, et al. *Lancet* 2014;383:955–962.

Use of low-dose DOACs in the real world vs. in clinical trials

Percentage of patients studied on an approved low-dose DOAC for stroke prevention in non-valvular AF in **clinical trials**:

49.7%

RE-LY[1]
(n=6,015/12,091)

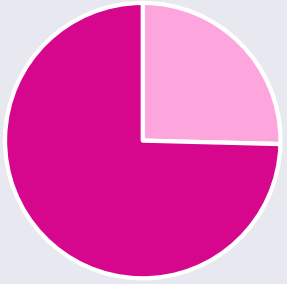


20.1%

ROCKET-AF[2]
(n=1,474/7,131)*

4.7%

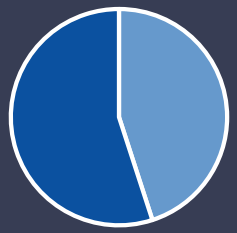
ARISTOTLE[3]
(n=428/9,120)*



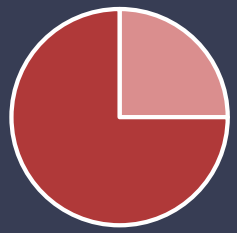
25.4%

ENGAGE AF-TIMI[4]
(n=1,784/7,035)*

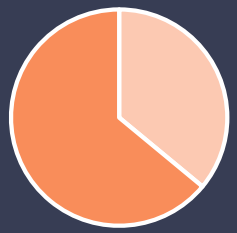
Percentage of **real-world** prescriptions of low-dose DOAC in the UK[5]:



45%



25%



36%

37%

- Pradaxa 110 mg b.d.
- Pradaxa 150 mg b.d.
- Rivaroxaban 15 mg o.d.
- Rivaroxaban 20 mg o.d.
- Apixaban 2.5mg b.d.
- Apixaban 5mg b.d.
- Edoxaban 30mg o.d.
- Edoxaban 60mg o.d.

*These patient populations received low-dose treatment following dose reductions based on specific patient criteria.

1. Connolly SJ, *et al. N Engl J Med* 2009;361:1139–1151; 2. Fox KA, *et al. Eur Heart J* 2011;32:2387–2394; 3. Granger CB, et al. *N Engl J Med* 2011;365:981–992; 4. Giugliano RP, *et al. N Engl J Med* 2013;369:2093–2104. 5.

RCTs and real-world research come together when making informed treatment decisions

Randomised clinical trials can provide:		Real-world data can provide:
High levels of **evidence**[1,2]	⟷	**Generalisable** results[1,2]
Controlled, randomised, unbiased populations[2]	⟷	Patients representative of **real clinical practice**[1,2]
Basis for regulatory **approval** of treatment[1]	⟷	Basis for **interpreting** clinical practice[1]
Basis for **treatment guidelines**[1]	⟷	Basis for generating **hypotheses**[1]

What does this mean?

Real-world data complement the results of RCTs by providing additional information that can be used to inform treatment decisions[1]

An independent, USA real-world analysis assessed the effectiveness and safety of DOACs vs warfarin for stroke prevention in NVAF[1]

- Non-interventional retrospective analysis using administrative claims from Optumlabs Data Warehouse database and Medicare Advantage
- The effectiveness and safety of apixaban (n=15,390), dabigatran (n=28,614)* and rivaroxaban (n=32,350) were compared with warfarin for stroke prevention in NVAF patients†
- The definitions of efficacy and safety endpoints in the ARISTOTLE, RE-LY and ROCKET-AF clinical trials differed to those in this study

Limitations of this real-world study‡

Results are derived from a population and healthcare system in the USA, and may not be generalisable to other healthcare systems, such as the UK

Insurance claims databases may contain incomplete or inaccurate data

There may be selection biases and other confounding factors due to lack of randomisation

**The 110 mg dose of dabigatran is not a licensed dose in the USA and so was not included in this real-world study.*
†This real-world study did not include edoxaban, as it was not FDA-approved during the time periods analysed.
‡For further details of the limitations of this analysis, please refer to the full publication.
FDA: US Food and Drug Administration.

1. Yao X, et al. *J Am Heart Assoc* 2016;5(6):pii: e003725.

Study endpoints: USA real-world analysis[1] and DOAC RCTs[2–4]

	Primary efficacy endpoint	Primary safety endpoint
USA real-world data analysis[1]	**Stroke (ischaemic or haemorrhagic) or SE** (Identified using ICD-9 codes in the primary or secondary diagnosis positions of inpatient claims)*	**Major bleeding** (Including GI bleeding, intracranial bleeding, and bleeding from other sites) (Identified using ICD-9 codes in the primary or secondary diagnosis positions of inpatient claims)
ARISTOTLE (RCT)[2]	**Stroke or SE** (Stroke was defined as a focal neurologic deficit from a non-traumatic cause, lasting at least 24 hours and was categorised as ischaemic [with or without haemorrhagic transformation], haemorrhagic, or of uncertain type in patients who did not undergo brain imaging or in whom an autopsy was not performed)	**Major bleeding** (Defined according to the ISTH criteria as clinically overt bleeding accompanied by a decrease in the haemoglobin level of ≥ 2g/dL or transfusion of ≥2 units of packed red cells, occurring at a critical site, or resulting in death)
RE-LY (RCT)[3]	**Stroke or SE** (Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorised as ischaemic, haemorrhagic, or unspecified)	**Major bleeding** (Defined as a reduction in the haemoglobin level of ≥20 g/L, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ)
ROCKET-AF (RCT)[4]	**Composite of stroke (ischaemic or haemorrhagic) and SE** (Brain imaging was recommended to distinguish haemorrhagic from ischemic stroke. In the presence of atherosclerotic peripheral arterial disease, the diagnosis of embolism required angiographic demonstration of abrupt arterial occlusion)	**Composite of major and nonmajor clinically relevant bleeding** (Defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site, fall in haemoglobin concentration of >2 units of whole blood or packed red blood cells, or permanent disability)

**The International Classification of Diseases, 9th Revision, was the system used for assigning codes to diagnoses and procedures associated with hospital utilisation in the USA.*
ICD: International Statistical Classification of Diseases and Related Health Problems.

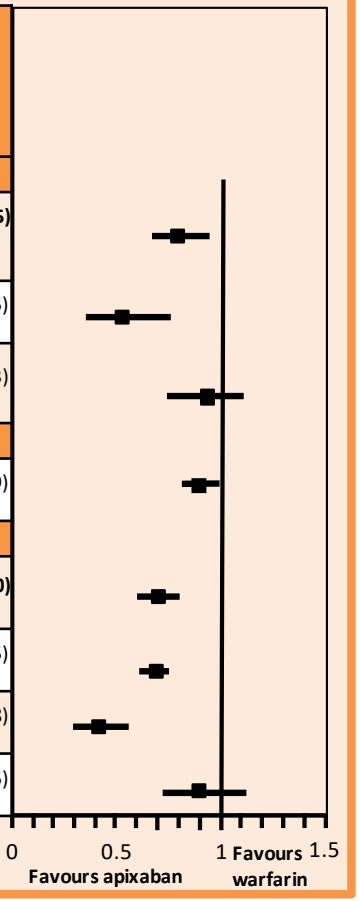
1. Yao X, et al. *J Am Heart Assoc* 2016;5(6):e003725; 2. Granger CB, et al. *N Engl J Med* 2011(11);365:981–992;
3. Connolly SJ, et al. *N Engl J Med* 2009;361(12):1139–1151; 4. Patel MR, et al. *N Engl J Med* 2011;365(10):883–891.

Apixaban demonstrated improved stroke/SE outcomes and improved major bleeding outcomes vs warfarin[1,2]

ARISTOTLE RCT[1]

Apixaban was superior to warfarin in preventing stroke, caused less major bleeding, and resulted in lower mortality

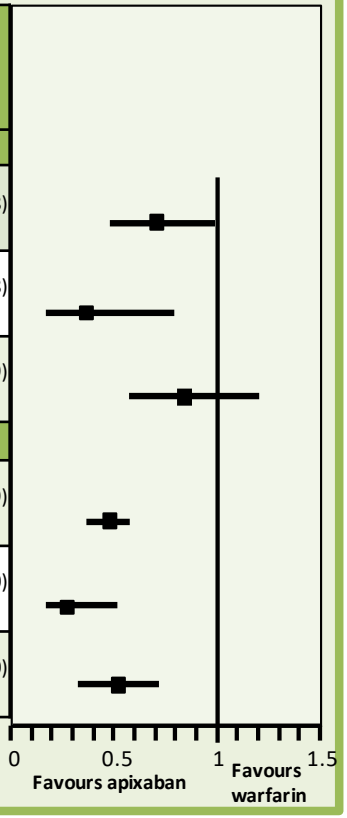
	Patients with event, n (event rate as %/year)		HR (95% CI)
	Apixaban (5 mg BD)* (n=9,120)	Warfarin (n=9,081)	
Primary efficacy outcome			
Stroke or SE[†]	**212 (1.27)**	**265 (1.60)**	**0.79 (0.66–0.95) *P*=0.01 (superiority)**
Haemorrhagic stroke	40 (0.24)	78 (0.47)	0.51 (0.35–0.75) *P*<0.001
Ischaemic or uncertain type of stroke	162 (0.97)	175 (1.05)	0.92 (0.74–1.13) *P*=0.42
Secondary efficacy outcome			
All-cause mortality[‡]	603 (3.52)	669 (3.94)	0.89 (0.80–0.99) *P*=0.047
Safety outcomes[§]			
Major bleeding[¶]	**327 (2.13)**	**462 (3.09)**	**0.69 (0.60–0.80) *P*<0.001**
Major/CRNM bleeding	613 (4.07)	877 (6.01)	0.68 (0.61–0.75) *P*<0.001
Intracranial bleeding	52 (0.33)	122 (0.80)	0.42 (0.30–0.58) *P*<0.001
GI bleeding	105 (0.76)	119 (0.86)	0.89 (0.70–1.15) *P*=0.37



USA real-world analysis[2]

Apixaban was associated with improved or comparable stroke outcomes vs warfarin and improved major bleeding outcomes vs warfarin

	Event rate (per 100 person-years)		HR (95% CI)
	Apixaban (n=7,695)[#]	Warfarin (n=7,695)[#]	
Primary effectiveness endpoints			
Stroke or SE	1.33	1.66	0.67 (0.46–0.98) *P*=0.04
Haemorrhagic stroke	0.19	0.46	0.35 (0.14–0.88) *P*=0.03
Ischaemic stroke	1.03	1.05	0.83 (0.53–1.29) *P*=0.40
Primary safety endpoints			
Major bleeding	2.33	4.46	0.45 (0.34–0.59) *P*<0.001
Intracranial bleeding	0.29	1.06	0.24 (0.12–0.50) *P*<0.001
GI bleeding	1.78	3.04	0.51 (0.37–0.70) *P*<0.001



For full study details and endpoint definitions, please refer to study publications. Please refer to product SmPCs for indications and dosing information

**The lower dose of apixaban 2.5 mg BD was used in a subset of patients with NVAF and an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg per deciliter (133 µmol per liter). As per the SmPC, Patients with the exclusive criteria of renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of 2.5 mg BD.[3] [†]This additional criterion differs from the trial conduct; [‡]Data from the ITT population (all patients who underwent randomisation) – follow-up continued until notification of study termination; [‡]All-cause mortality data presented based on ITT population; [§]The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through to 2 days after they received the last dose; [¶]Primary safety outcome; [#]N numbers are based on 1:1 propensity score matching in this real-world study.*
GI: gastrointestinal; HR: hazard ratio.

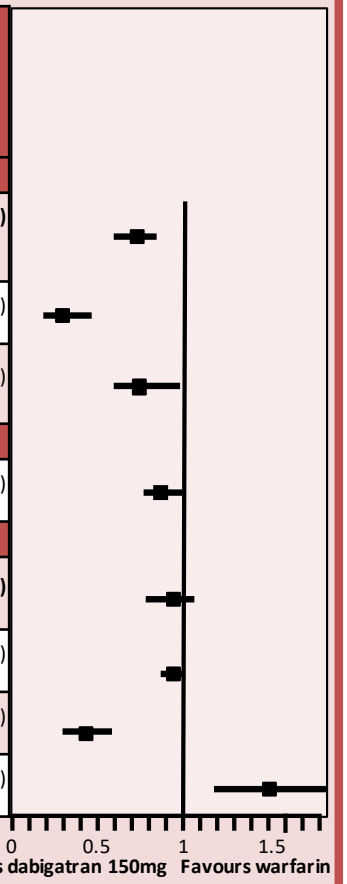
1. Granger CB, et al. *N Engl J Med* 2011(11);365:981–992;
2. Yao X, et al. *J Am Heart Assoc* 2016;5(6):e003725;
3. Apixaban SmPC. Available at: http://www.medicines.org.uk.

Dabigatran 150 mg BD demonstrated improved or comparable stroke and major bleeding outcomes vs warfarin[1–4]

RE-LY RCT[1–3]

Dabigatran (150 mg BD), compared with warfarin, was associated with lower rates of stroke and SE but similar rates of major bleeding

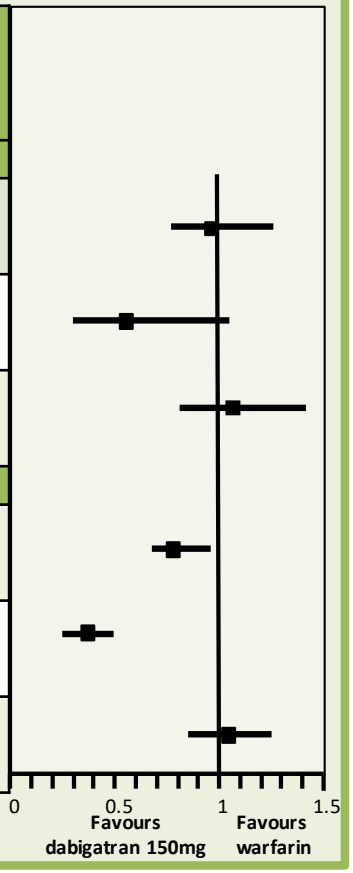
	Patients with event, n (%/year)		RR (95% CI)
	Dabigatran 150 mg BD (n=6,076)	Warfarin (n=6,022)	
Primary efficacy outcome*			
Stroke or SE[†1]	**135 (1.12)**	**203 (1.72)**	**0.65 (0.52–0.81) *P*<0.001 (superiority)**
Haemorrhagic stroke[†2]	12 (0.10)	45 (0.38)	0.26 (0.14–0.49) *P*<0.001
Ischaemic or unspecified stroke[1]	112 (0.93)	144 (1.22)	0.76 (0.59–0.97) *P*=0.03
Secondary efficacy outcome			
All-cause mortality[2]	438 (3.64)	487 (4.13)	0.88 (0.77–1.00) *P*=0.051
Safety outcomes*[‡]			
Major bleeding[§1]	**409 (3.40)**	**426 (3.61)**	**0.94 (0.82–1.08) *P*=0.41**
Major/minor bleeding[3]	1993 (16.56)	2166 (18.37)	0.91 (0.85–0.96) *P*=0.002
Intracranial bleeding[3]	38 (0.32)	90 (0.76)	0.41 (0.28–0.60) *P*<0.001
Major GI bleeding[3]	188 (1.56)	126 (1.07)	1.48 (1.18–1.85) *P*=0.001



USA real-world analysis[4]

Dabigatran (150 mg BD[ϕ]) demonstrated comparable **stroke outcomes** vs warfarin, improved **major and intracranial bleeding outcomes** vs warfarin, and comparable rates of GI bleeding outcomes

	Event rate per 100 person-year		HR (95% CI)
	Dabigatran (n=14,307)[¶]	Warfarin (n=14,307)[¶]	
Primary effectiveness endpoints			
Stroke or SE	1.18	1.22	0.98 (0.76–1.26) *P*=0.88
Haemorrhagic stroke	0.16	0.29	0.56 (0.30–1.04) *P*=0.07
Ischaemic stroke	0.92	0.88	1.06 (0.79–1.42) *P*=0.70
Primary safety endpoints			
Major bleeding	2.37	3.03	0.79 (0.67–0.94) *P*<0.01
Intracranial bleeding	0.28	0.79	0.36 (0.23–0.56) *P*<0.001
GI bleeding	1.97	1.95	1.03 (0.84–1.26) *P*=0.78



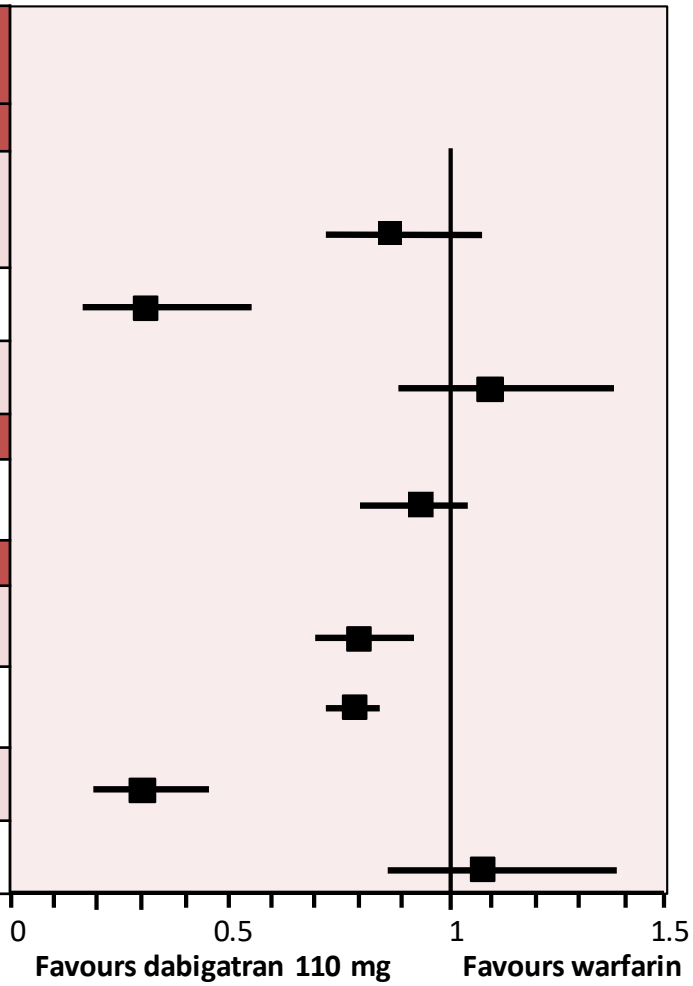
For full study details, please refer to study publications. Please refer to product SmPCs for indications and dosing information

**Efficacy and safety results are based on ITT population, data are shown for all patients who had at least one event, and all analyses are based on the time to the first event; [†]Haemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis was also counted as major, life-threatening bleeding, and as part of intracranial bleeding; [‡]The composite of major bleeding and CRNM bleeding was not specified; [§]Primary safety outcome; [ϕ]Dabigatran 110 mg BD is not an approved dose in the USA; [¶]N numbers are based on 1:1 propensity score matching in this real-world study.*

1. Connolly SJ, et al. *N Engl J Med* 2014:371(15):1464–1465; 2. Connolly SJ, et al. *N Engl J Med* 2009;361(12):1139–1151;
3. Connolly SJ, et al. *N Engl J Med 2010*;363(19):1875–1876 and supplementary appendix;
4. Yao X, et al. *J Am Heart Assoc* 2016;5(6):pii: e003725.

Dabigatran 110 mg BD: Similar rates of stroke/SE to warfarin and lower rates of major bleeding demonstrated in the RE-LY RCT[1–3]

	Dabigatran 110 mg (n=6,015)	Warfarin (n=6,022)	RR (95% CI)	*P* value
Primary efficacy outcome*				
Stroke or systemic embolism, n (%/year)[1]	**183 (1.54)**	**203 (1.72)**	**0.89 (0.73–1.09)**	**<0.001 (non-inferiority)**
– Haemorrhagic stroke, n (%/year)[†2]	14 (0.12)	45 (0.38)	0.31 (0.17–0.56)	<0.001
– Ischaemic or unspecified stroke, n (%/year)[1]	159 (1.34)	144 (1.22)	1.10 (0.88–1.37)	0.42
Secondary efficacy outcome*				
All-cause mortality, n (%/year)[2]	446 (3.75)	487 (4.13)	0.91 (0.80–1.03)	0.13
Safety outcomes*‡				
Major bleeding,[§] n (%/year)[1]	**347 (2.92)**	**426 (3.61)**	**0.80 (0.70–0.93)**	**0.003**
Major or minor bleeding, n (%/year)[3]	1,754 (14.74)	2,166 (18.37)	0.78 (0.73–0.83)	<0.001
Intracranial bleeding, n (%/year)[3]	27 (0.23)	90 (0.76)	0.30 (0.19–0.45)	<0.001
Major GI bleeding, n (%/year)[3]	137 (1.15)	126 (1.07)	1.08 (0.85–1.38)	0.52



**Efficacy and safety results are based on ITT population, data are shown for all patients who had at least one event, and all analyses are based on the time to the first event; †Haemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis was also counted as major, life-threatening bleeding, and as part of intracranial bleeding; ‡The composite of major bleeding and non-major clinically relevant bleeding was not specified; §Primary safety outcome.*

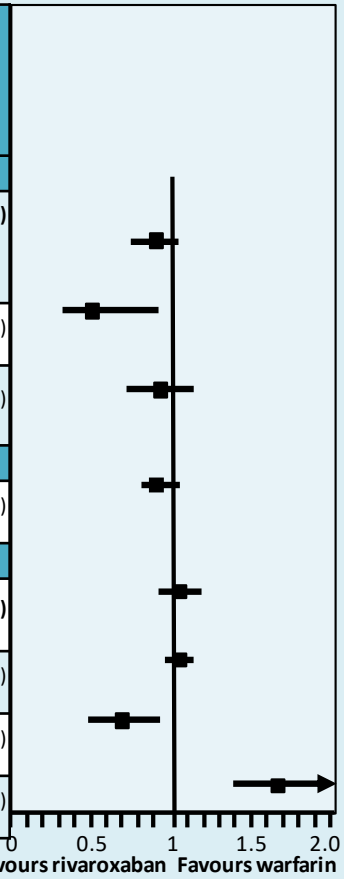
1. Connolly SJ, et al. *N Engl J Med* 2014;371(15):1464–1465; 2. Connolly SJ, et al. *N Engl J Med* 2009;361(12):1139–1151; 3. Connolly SJ, et al. *N Engl J Med* 2010;363(19):1875–1876 and supplementary appendix.

Rivaroxaban demonstrated comparable stroke and major bleeding outcomes vs warfarin[1–3]

ROCKET-AF RCT[1,2]

Rivaroxaban (20 mg OD) was non-inferior to warfarin for the prevention of stroke or SE, with no significant difference in the risk of major bleeding

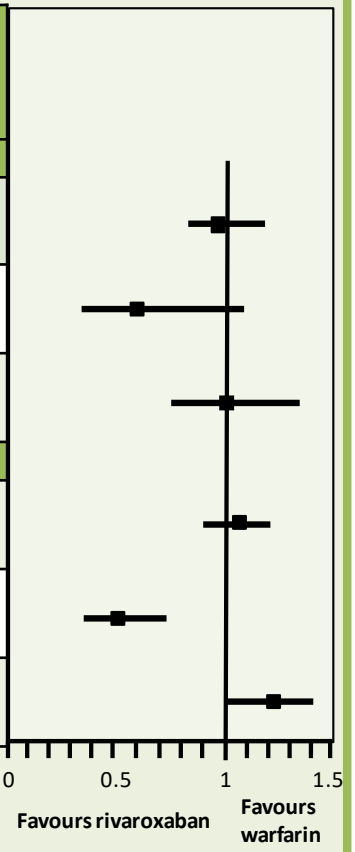
	Number of events (no./100 patient-years)		RR (95% CI)
	Rivaroxaban (20 mg OD)* (n=7,131)	Warfarin (n=7,133)	
Primary efficacy outcome			
Stroke or SE[†1]	**269 (2.1)**	**306 (2.4)**	**0.88 (0.75–1.03) *P*<0.001 (non-inferiority)**
Haemorrhagic stroke[‡1]	29 (0.26)	50 (0.44)	0.59 (0.37–0.93) *P*=0.024
Ischaemic or unspecified stroke[‡1]	149 (1.34)	161 (1.42)	0.94 (0.75–1.17) *P*=0.581
Secondary efficacy outcome			
All-cause mortality*[1]	582 (4.5)	632 (4.9)	0.92 (0.82–1.03) *P*=0.15
Safety outcomes[‡§]	**RR**		
Major bleeding[¶1]	**395 (3.6)**	**386 (3.4)**	**1.04 (0.90–1.20) *P*=0.58**
Major and CRNM bleeding[1]	1475 (14.9)	1449 (14.5)	1.03 (0.96–1.11) *P*=0.44
Intracranial bleeding[1]	55 (0.5)	84 (0.7)	0.67 (0.47–0.93) *P*=0.02
Major GI bleeding[ϕ2]	221 (2.00)	140 (1.24)	1.66 (1.34–2.05) *P*<0.0001



USA real-world analysis[3]

Rivaroxaban was associated with comparable **stroke outcomes** and **major bleeding outcomes** vs warfarin

	Event rate per 100 person-year		HR (95% CI)
	Rivaroxaban (n=16,175)[#]	Warfarin (n=16,175)[#]	
Primary effectiveness endpoints			
Stroke or SE	1.26	1.29	0.93 (0.72–1.19) *P*=0.56
Haemorrhagic stroke	0.21	0.32	0.61 (0.35–1.07) *P*=0.08
Ischaemic stroke	0.95	0.88	1.01 (0.75–1.36) *P*=0.95
Primary safety endpoints			
Major bleeding	4.04	3.64	1.04 (0.90–1.20) *P*=0.60
Intracranial bleeding	0.44	0.79	0.51 (0.35–0.75) *P*<0.001
GI bleeding	3.26	2.53	1.21 (1.02–1.43) *P*=0.03



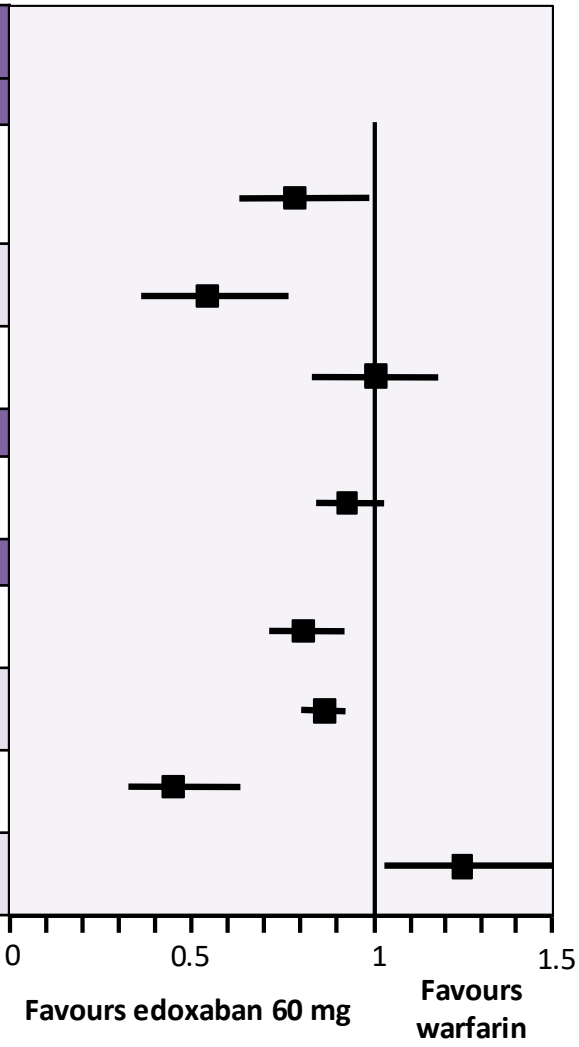
For full study details, please refer to study publications. Please refer to product SmPCs for indications and dosing information

**A dose of 15 mg OD was used in patients with NVAF and a creatinine clearance of 30–49 mL per minute. As per the SmPC, a dose of 15 mg is recommended in patients with NVAF who have one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack;[4] †Efficacy results are based on the ITT population (all patients who underwent randomisation): follow-up continued until notification of study termination; ‡Analysis of bleeding events was performed on the basis of the number of patients treated with rivaroxaban (7,111) or warfarin (7,125), rather than the number assigned to the treatment; §Safety results are based on the safety population, which included patients who received at least one dose of a study drug and were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within 2 days after discontinuation; ¶The primary safety outcome was a composite of major and non-major clinically relevant bleeding events; ϕMajor GI bleeding rates are the result of a post-hoc non-randomised subgroup analysis of data obtained during the ROCKET-AF trial;[2] #N numbers are based on 1:1 propensity score matching in this real-world study.*

1. Patel MR, et al. *N Engl J Med* 2011;365(10):883–891 and supplementary appendix;
2. Sherwood MW, et al. *J Am Coll Cardiol* 2015;66(21):2271–2281;
3. Yao X, et al. *J Am Heart Assoc* 2016;5(6):pii: e003725;
4. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk.

Edoxaban 60 mg OD was non-inferior to warfarin with respect to the prevention of stroke or SE with significantly lower rates of major bleeding in the ENGAGE AF-TIMI 48 RCT[1]

	Edoxaban (n=7,036)	Warfarin (n=7,035)	HR (95% CI)	*P* value
Primary efficacy outcome				
Stroke/SE n (%/year)*	**182 (1.18)**	**232 (1.50)**	**0.79 (0.63–0.99)**	**<0.001 (non-inferiority)**
– Haemorrhagic stroke, n (%/year)	49 (0.26)	90 (0.47)	0.54 (0.38–0.77)	<0.001
– Ischaemic stroke, n (%/year)	236 (1.25)	235 (1.25)	1.00 (0.83–1.19)	0.97
Other efficacy outcomes				
All-cause mortality, n (%/year)	773 (3.99)	839 (4.35)	0.92 (0.83–1.01)	0.08
Safety outcomes†				
Major bleeding, n (%/year)‡	**418 (2.75)**	**524 (3.43)**	**0.80 (0.71–0.91)**	**<0.001**
Major or CRNM bleeding, n (%/year)	1,528 (11.10)	1,761 (13.02)	0.86 (0.80–0.92)	<0.001
Intracranial bleeding, n (%/year)	61 (0.39)	132 (0.85)	0.47 (0.34–0.63)	<0.001
Major GI bleeding, n (%/year)	232 (1.51)	190 (1.23)	1.23 (1.02–1.50)	0.03



**Modified ITT population (patients who underwent randomisation and received at least one dose of the study drug during the treatment period). The analysis of the modified ITT population included data from 7,012 patients in the warfarin group and 7,012 in the edoxaban group. 97.5% CI was used for the primary efficacy endpoint; †The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug, with interval censoring of events occurring during study drug interruptions of >3 days' duration. ‡Major bleeding was the primary safety outcome and was adjudicated in accordance with the ISTH criteria.*

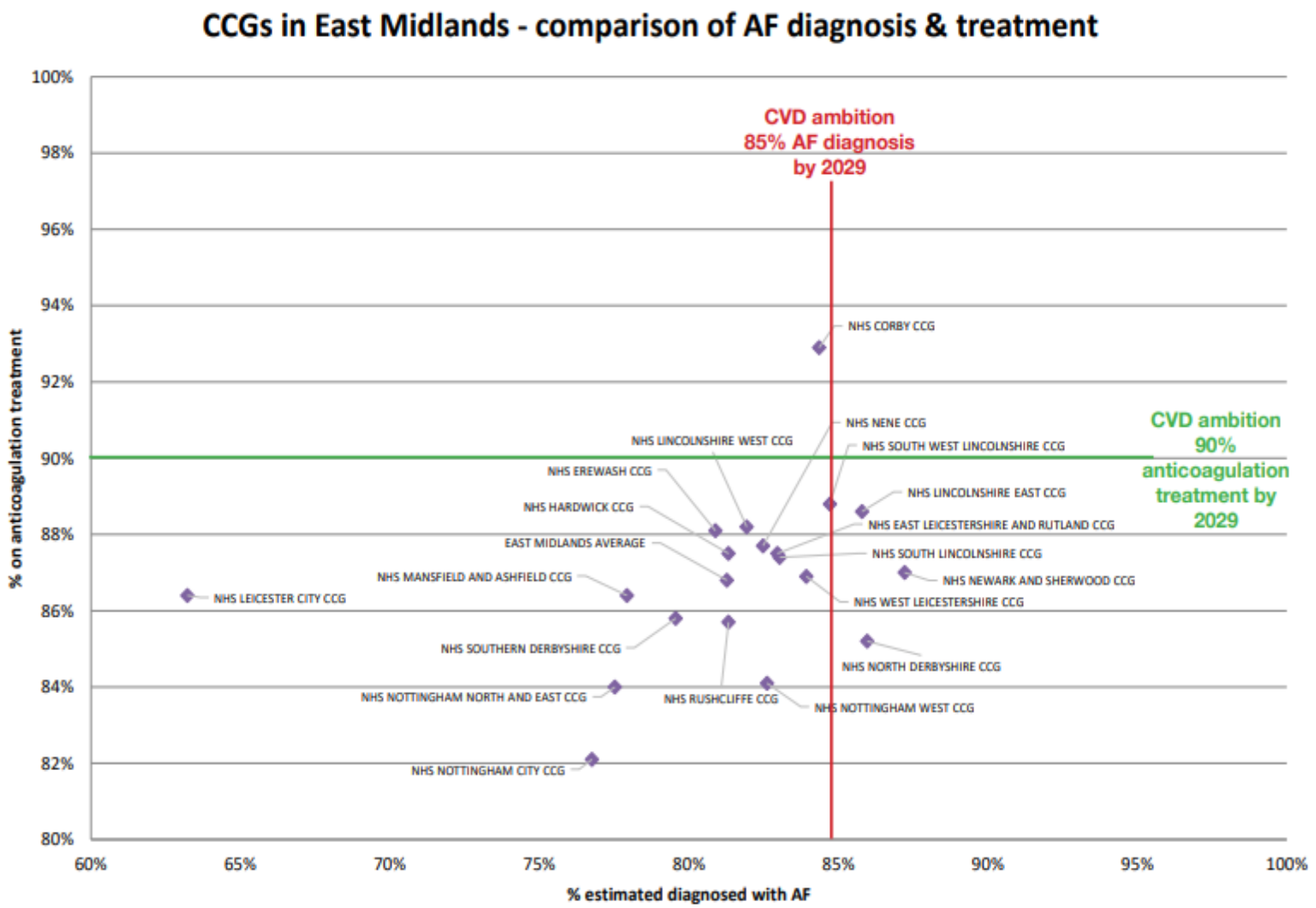
1. Giugliano RP, et al. *N Engl J Med* 2013;369(22):2093–2104.

Comparison of AF diagnosis and anticoagulation treatment within CCGs in East Midlands

Key:
- Below East Midlands Average
- Below National CVD Ambition
- Meet National CVD Ambition

		DETECT % AF diagnosis March 2018	PROTECT % Anticoagulation Treatment March 2018
DERBYSHIRE STP	NHS SOUTHERN DERBYSHIRE CCG	79.6%	85.8%
	NHS EREWASH CCG	80/9%	88.1%
	NHS HARDWICK CCG	81.3%	87.5%
	NHS NORTH DERBYSHIRE CCG	86.0%	85.2%
LINCOLNSHIRE STP	NHS LINCOLNSHIRE WEST CCG	81.9%	88.2%
	NHS SOUTH LINCOLNSHIRE CCG	83.0%	87.4%
	NHS SOUTH WEST LINCOLNSHIRE CCG	84.7%	88.8%
	NHS LINCOLNSHIRE EAST CCG	85.8%	88.6%
LEICESTER, LEICESTERSHIRE & RUTLAND STP	NHS LEICESTER CITY CCG	63.2%	86.4%
	NHS EAST LEICESTERSHIRE AND RUTLAND CCG	83.6%	87.5%
	NHS WEST LEICESTERSHIRE CCG	83.9%	86.9%
NORTHAMPTONSHIRE STP	NHS CORBY CCG	84.4%	92.9%
	NHS NENE CCG	82.5%	87.7%
NOTTINGHAMSHIRE STP	NHS NOTTINGHAM CITY CCG	76.8%	82.1%
	NHS NOTTINGHAM NORTH AND EAST CCG	77.5%	84.0%
	NHS MANSFIELD AND ASHFIELD CCG	77.9%	86.4%
	NHS RUSHCLIFFE CCG	81.3%	85.7%
	NHS NOTTINGHAM WEST CCG	82.6%	84.1%
	NHS NEWARK AND SHERWOOD CCG	87.2%	87.0%
EAST MIDLANDS		81.3%	86.8%

CCGs in East Midlands - comparison of AF diagnosis & treatment


CCGs in East Midlands - comparison of AF diagnosis & treatment
CVD ambition
85% AF diagnosis
by 2029
CVD ambition
90%
anticoagulation
treatment by
2029
NHS CORBY CCG
NHS NENE CCG
NHS LINCOLNSHIRE WEST CCG
NHS SOUTH WEST LINCOLNSHIRE CCG
NHS EREWASH CCG
NHS LINCOLNSHIRE EAST CCG
NHS HARDWICK CCG
NHS EAST LEICESTERSHIRE AND RUTLAND CCG
EAST MIDLANDS AVERAGE
NHS SOUTH LINCOLNSHIRE CCG
NHS MANSFIELD AND ASHFIELD CCG
NHS NEWARK AND SHERWOOD CCG
NHS LEICESTER CITY CCG
NHS WEST LEICESTERSHIRE CCG
NHS SOUTHERN DERBYSHIRE CCG
NHS NORTH DERBYSHIRE CCG
NHS NOTTINGHAM NORTH AND EAST CCG
NHS RUSHCLIFFE CCG
NHS NOTTINGHAM WEST CCG
NHS NOTTINGHAM CITY CCG
% on anticoagulation treatment
100%
98%
96%
94%
92%
90%
88%
86%
84%
82%
80%
60%
65%
70%
75%
80%
85%
90%
95%
100%
% estimated diagnosed with AF

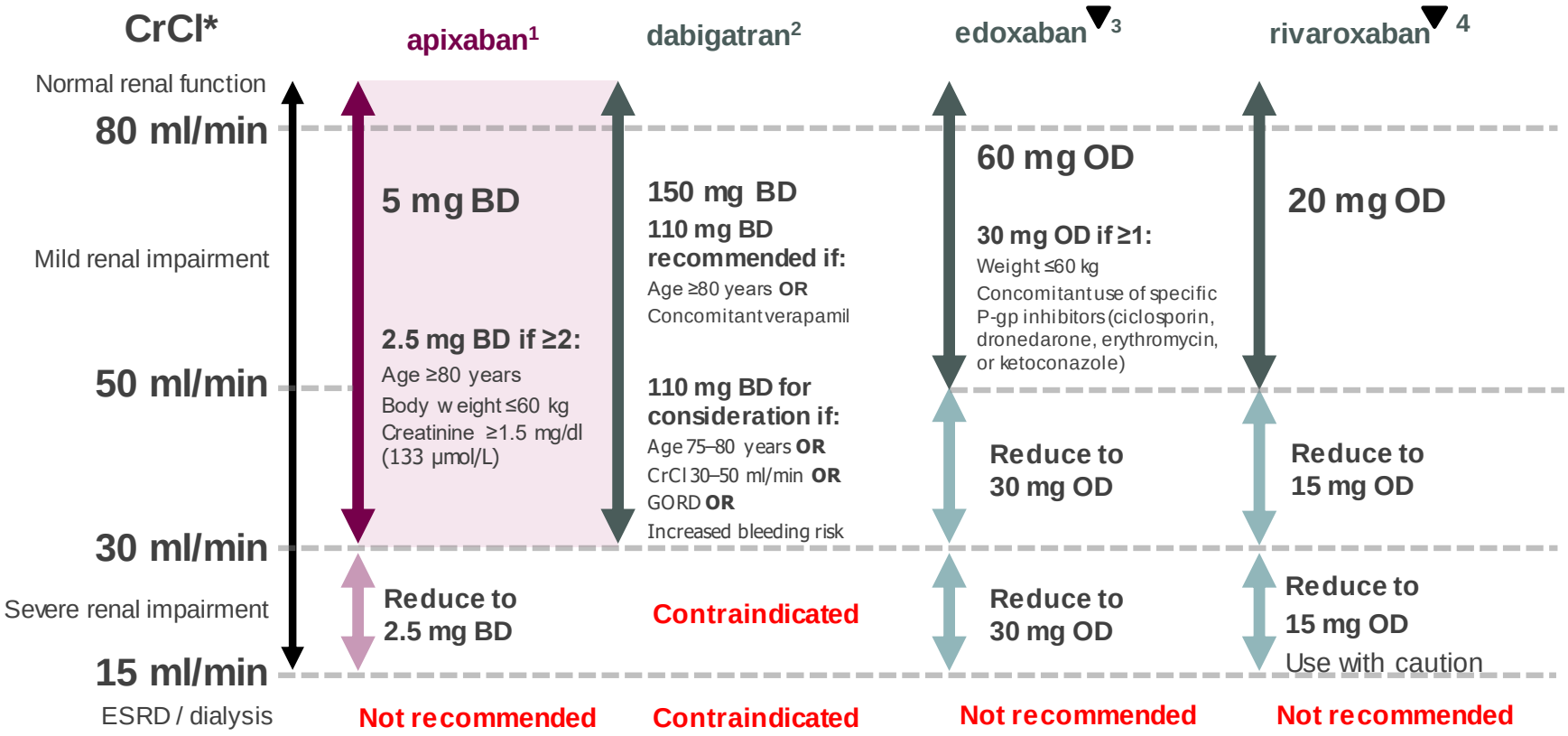
Specifics re different DOACs

- NICE CKD in adults (CG182, 2014)1
  - "Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 mL/min/1.73 m2 and non-valvular atrial fibrillation who have one or more of the following risk factors:
    - Prior stroke or transient ischaemic attack
    - Age ≥75 years
    - Hypertension
    - Diabetes mellitus
    - Symptomatic heart failure"
- Rivaroxaban should be taken with food
- Dabigatran cannot be crushed, so unsuitable if patient is on tube feeding
- There is no published RWE for Edoxaban yet
- More evidence for Apix 5mg bd in comparison with 2.5mg bd
- **Be very careful using DOACs if CrCl in 20s**
- Check CrCl regularly depending on baseline (4 monthly if in 40s, 3 monthly in 30s and at least alternate months if in 20s)

Please refer to the SmPCs of individual drugs for more detailed information.

Specifics re different DOACs

NOAC dosage guidance in patients with NVAF according to renal function[1–5]



Adapted from Steffel *et al*. 2018.[5]

Please refer to the SmPCs of individual drugs for more detailed information on dosing.

A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high CrCl after a careful evaluation of the individual thromboembolic and bleeding risk.

*CrCl was calculated using the Cockcroft-Gault equation in the phase III clinical trials for each NOAC. Therefore, dosing of NOACs should be based on CrCl as per the respective SmPCs. Mild renal impairment is defined as CrCl 51–80 ml/min for ELIQUIS, and 50–80 ml/min for rivaroxaban, dabigatran, and edoxaban; moderate renal impairment is defined as 30—50 ml/min for ELIQUIS, dabigatran, and edoxaban, and 30–49 ml/min for rivaroxaban; severe renal impairment is defined as 15–29 ml/min for ELIQUIS, rivaroxaban, and edoxaban and <30 ml/min for dabigatran.1–4

1. ELIQUIS (apixaban) SmPC Available at www.medicines.org.uk. 2. Xarelto (rivaroxaban) SmPC. Available at www.medicines.org.uk.
3. Pradaxa (dabigatran) SmPC. Available at www.medicines.org.uk 4. Lixiana (edoxaban) SmPC. Available at www.medicines.org.uk. 5. Steffel J et al. Eur Heart J 2018; 39: 1330–1393.

Antidotes

- Idarucizumab (Praxbind) – monoclonal antibody available for dabigatran reversal. Indicated in adult patients treated with dabigatran when rapid reversal of its anticoagulant effects is required:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding.

- For Anti Xa agents – Andexanet alfa (Ondexxya) is licensed for adult patients treated with apixaban or rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding (but not licenced for edoxaban yet).

- **But ultimately, very few would need these in any case (none are licenced for usage pre-thrombolysis at this stage).**

Lifestyle advice

- Smoking cessation
- Alcohol reduction
- Exercise
- Low fat, low salt diet

Driving

- Must not drive for at least 28 days
- No need to inform DVLA
- Recurrent attacks over short time period
- 3 months off the road
- Must inform DVLA
- Should inform car insurance company

Carotid Surgery

- Severe stenosis (50-99%) and recent nondisabling stroke or TIA
  - -refer for surgical assessment within 1 week
  - -surgery within 2 weeks
- Carotid endarterectomy - LA

Summary

- TIAs can be difficult to diagnose – good history is crucial
- High risk of stroke
- Rapid assessment and management is vital