New (Direct)Oral anti-coagulants

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Declaration of interests

Received small lecturing fees from:

- Boehringer Ingelheim
- Bayer
- Bristol-Myers Squibb

- No shareholding or direct employment in pharmaceutical industry

NOACs

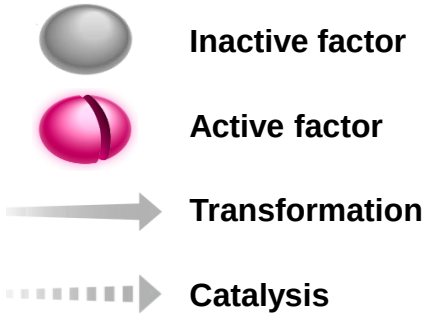
- What are they
- Are they good
- Are they safe
- How much are we using
- How much will we be using

New Oral Anticoagulants (NOAC)

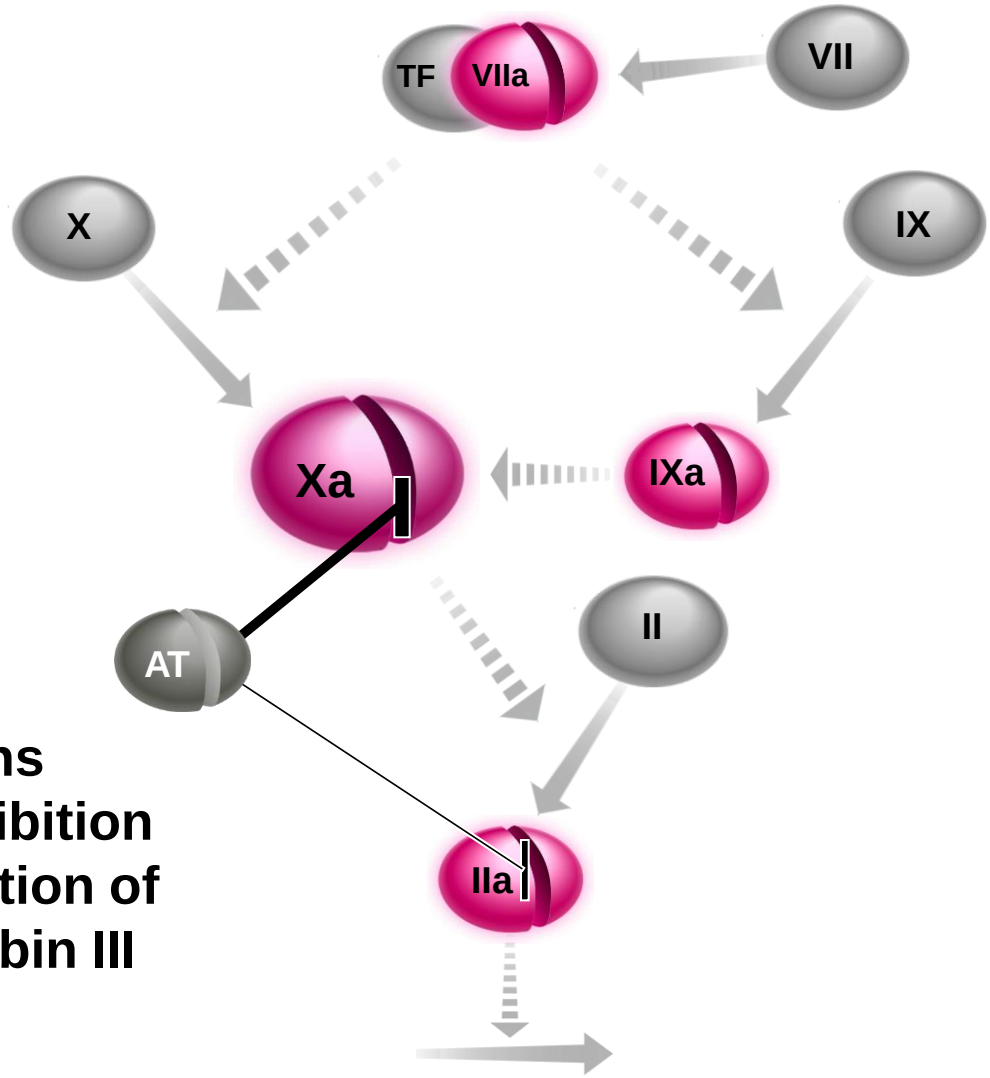
- Dabigatran - NICE (SPAF) March 2012
  NICE (VTE) Dec 2014
- Rivaroxaban - NICE (SPAF) May 2012
  NICE (VTE) July 2012
  NICE (ACS) March 2015
- Apixaban - NICE (SPAF) Feb 2013
  NICE (VTE) June 2015
- Edoxaban - NICE (SPAF) ?SEPT 2015
  (VTE) Aug 2015

Old drugs

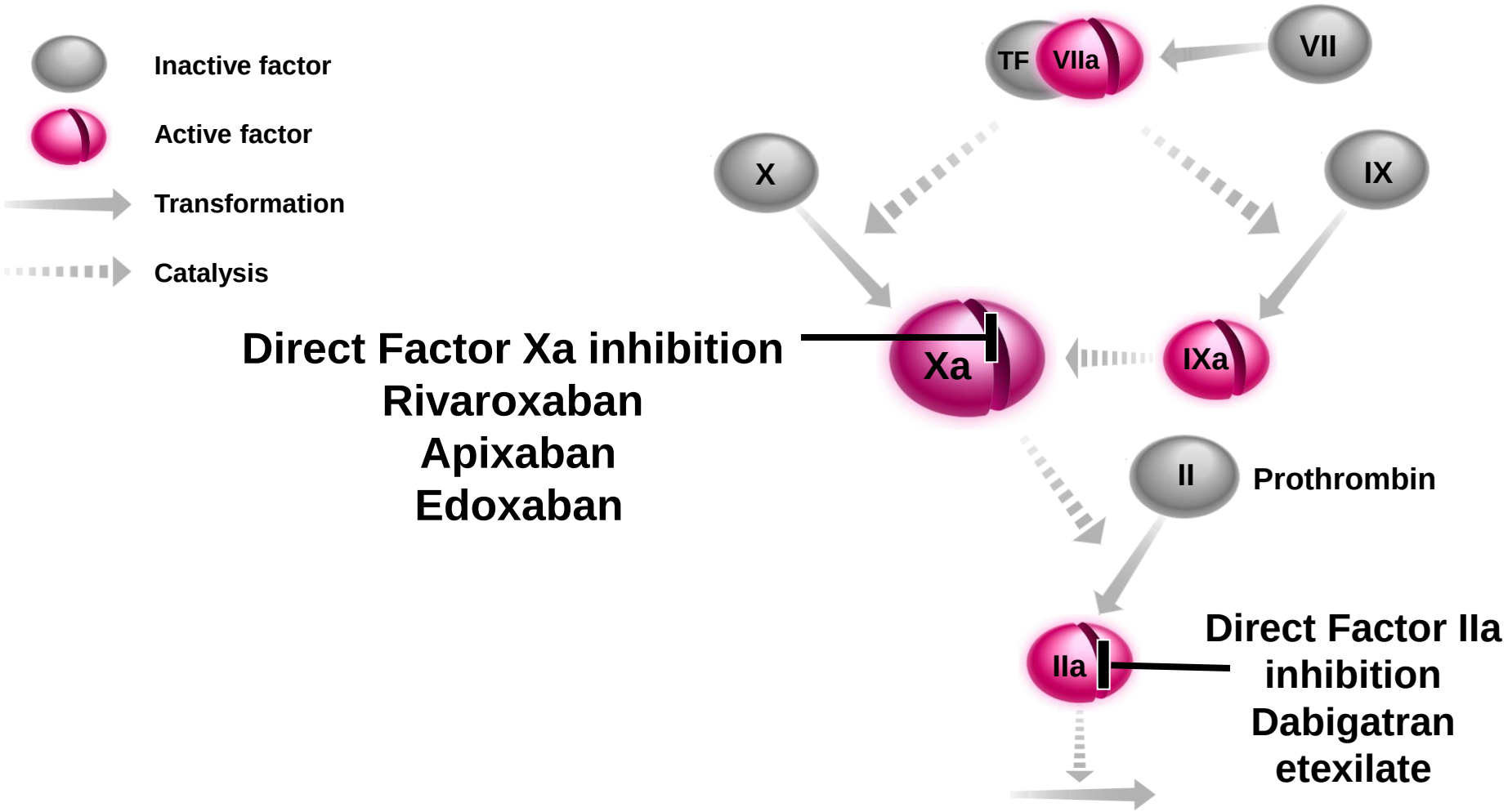
Warfarin (VKA's)
Reduction in production of factors II, VII, IX and X



Heparins
Indirect inhibition via potentiation of Anti-thrombin III



Direct Factor IIa & Xa inhibitors DOACs or NOAC's!



Adapted from Spyropoulos AC. *Expert Opin Investig Drugs* 2007;16:431–440

Clinical pharmacology of NOACs

	Apixaban[1,2]	Rivaroxaban[1,3]	Dabigatran[1,4]	Edoxaban[5]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor
Oral bioavailability	~50%	80–100%	~6.5%	~62%
Pro-drug	No	No	Yes	No
Food effect	No	Yes (20 mg and 15 mg doses need to be taken with food)	No	No
Renal clearance	~27%	~33 %*	85%	50%†
Mean half-life ($t_{1/2}$)	12 h	5–9 h (young) 11–13 h (elderly)	12–18 h (patients)‡	10–14 h
T_{max}	3–4 h	2–4 h	0.5–2 h	1–2 h

**Direct renal excretion as unchanged active substance.*
‡ Prolonged in patients with impaired renal function. † 35% of administered dose

SmPC for apixaban, rivaroxaban, dabigatran and edoxaban.
Please refer to the SmPC for further information.

Introduction to atrial fibrillation

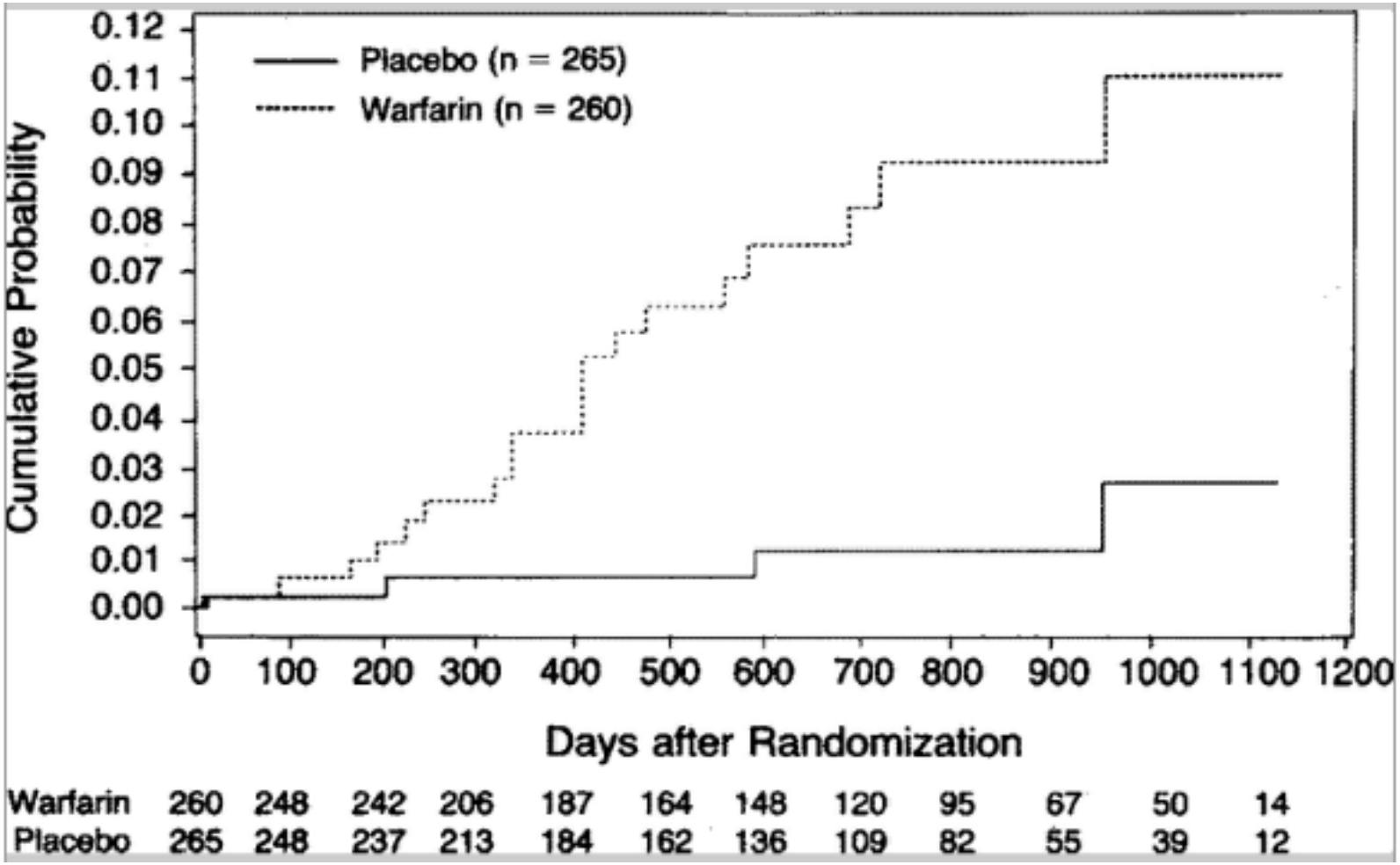
The NEW ENGLAND JOURNAL of MEDICINE

Warfarin in the Prevention of Stroke Associated with Non-rheumatic Atrial Fibrillation

- Michael D. Ezekowitz, M.D., Ph.D., Samuel L. Bridgers, M.D., Kenneth E. James, Ph.D., Nathan H. Carliner, M.D., Cindy L. Colling, R.Ph., M.S., Charles C. Gornick, M.D., Heidi Krause-Steinrauf, M.S., John F. Kurtzke, M.D., Sarkis M. Nazarian, M.D., Martha J. Radford, M.D., Frederick R. Rickles, M.D., Ralph Shabetai, M.D., Daniel Deykin, M.D., and the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators*

Ezekowitz, M.D et al, N Engl J Med 1992; 327:1406-1412 November 12, 1992

Cumulative probability of cerebral infarction

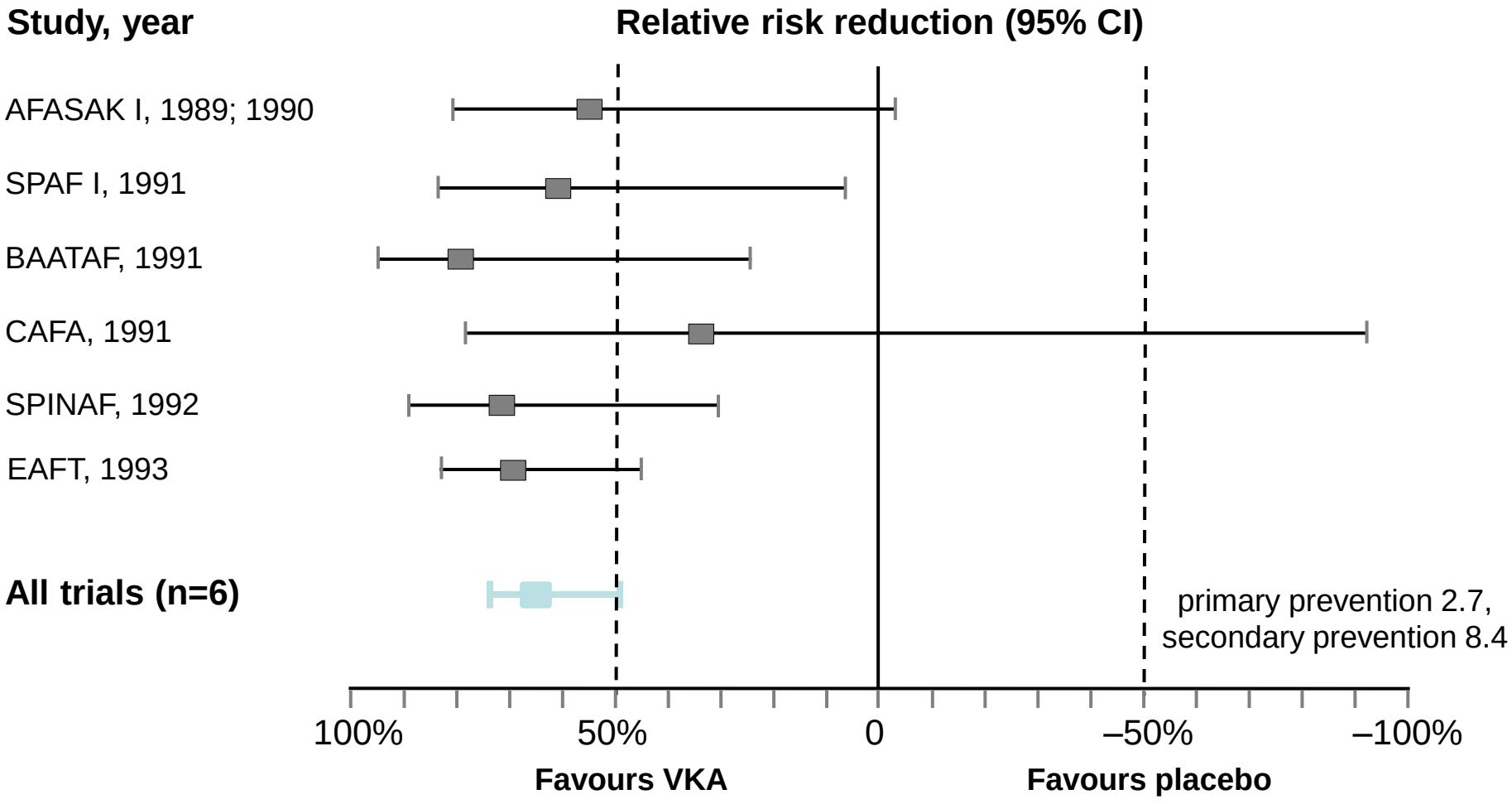


Risk reduction 0.79 p=0.001

Ezekowitz, M.D et al, N Engl J Med 1992; 327:1406-1412 November 12, 1992

Oral anti-coagulation for stroke prevention in AF

Reduction of risk of thromboembolism in AF[1]



Hart RG *et al*. *Ann Intern Med* 2007;146:857–867

AF: most common sustained cardiac arrhythmia

- Prevalence in the general population — 1–2%
- Europeans suffer from AF, including 800,000 in the UK[2] — >6 million[1]
- Greater risk in men than women — 1.4 x
- Lifetime risk in those who reach 40 years of age[1] — ~25%

AF: morbidity and mortality

- AF increases risk of mortality and morbidity due to:
  - Stroke and thromboembolism
  - Congestive heart failure
  - Impaired quality of life
- In the general population, AF is responsible for 20% of all strokes

- Strokes due to AF are associated with increased risk of death
  - 30-day mortality rate of 33% (vs 16% non-AF CVA)
  - 1-yr mortality rate 50% (vs 27% patients without AF)

Burden of AF and related stroke

- Estimated annual burden of AF (2008 data):

Total direct cost to NHS	£2.2 billion
5.7 million hospital bed days	*£1.8 billion*
Non-bed inpatient costs	*£124 million*
Outpatient costs	*£205 million*

- **Direct costs of stroke to NHS = c £2.8 billion**

- AF is responsible for 20% of all strokes
  - AF-related strokes are more severe
  - Severe strokes are >3x more costly on average than typical mild strokes

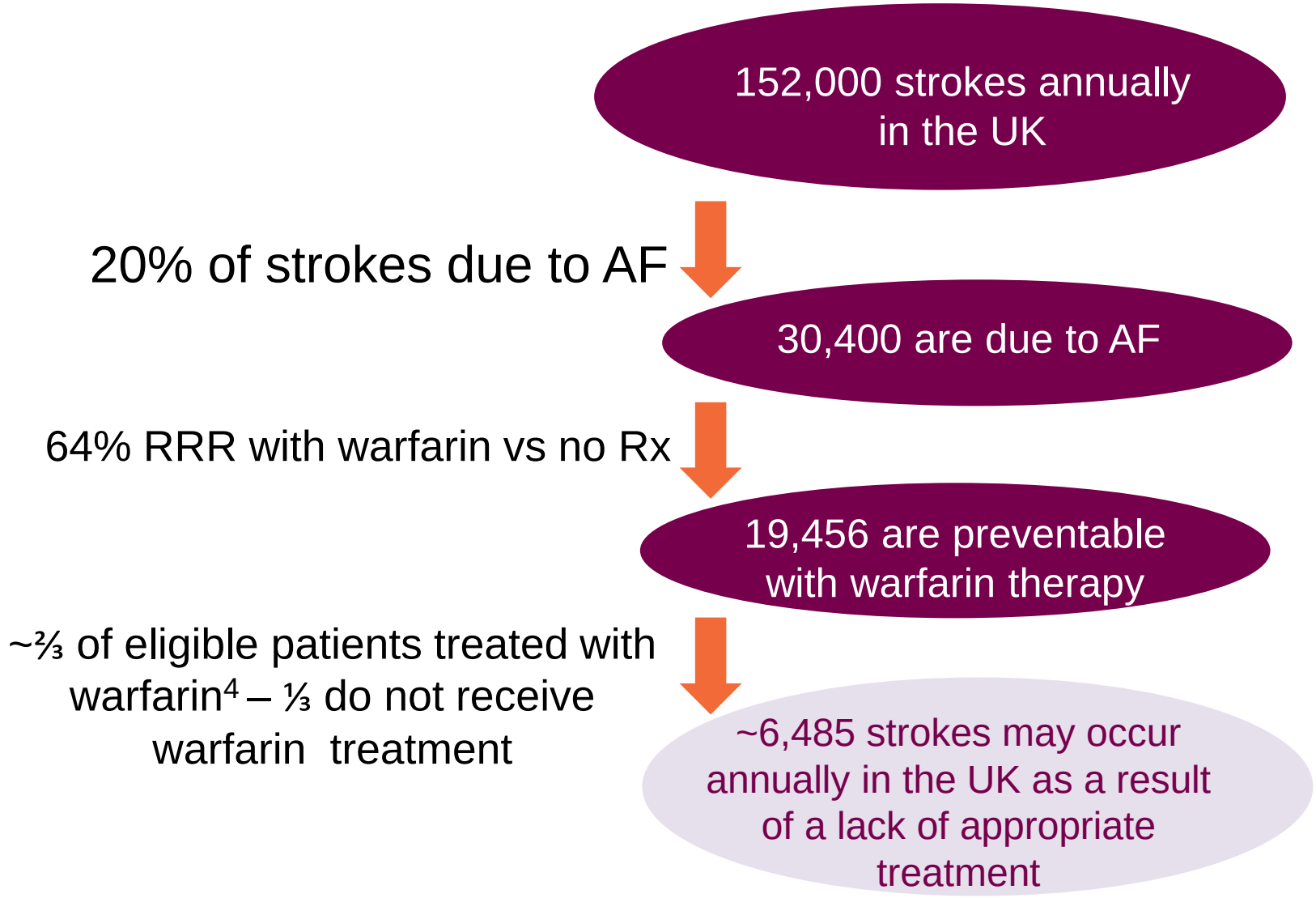
Types of atrial fibrillation – NVAF and VAF

- AF described as **valvular** (VAF) or **non-valvular** (NVAF)

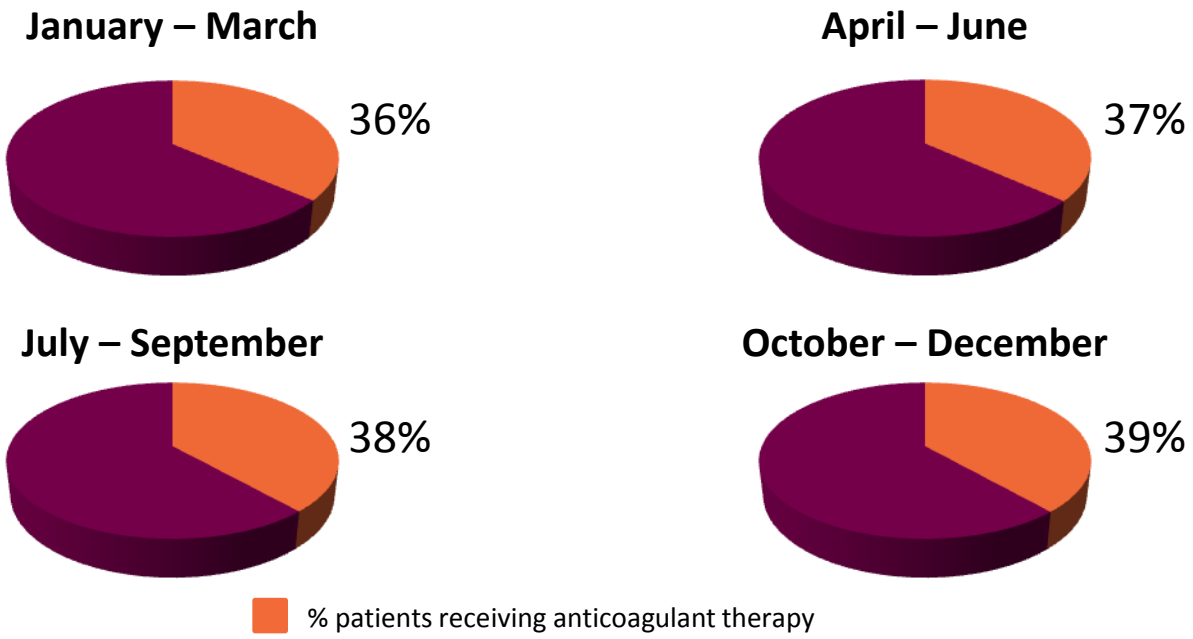
ESC Guidelines state:
"The term VAF is used to imply that AF is related to rheumatic valvular disease – predominantly mitral stenosis – or prosthetic heart valves"

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

Effective AF treatment:



Use of anticoagulant therapy in patients with AF admitted for a stroke



Sentinel Stroke National Audit Programme (SSNAP). Clinical audit October – December 2013 public report. National results. May 2014

Estimating stroke and bleeding risk in NVAF

Estimating stroke risk in NVAF: CHA_2DS_2-VASc

- CHA_2DS_2VASc – recommended in the 2014 NICE guidelines[1] and the 2012 ESC guidelines[2]

CHA_2DS_2-VASc stroke risk criteria[3]	Score
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65–74 years	1
Sex **c**ategory (i.e. female gender)	1
Maximum score	**9**

Adapted from Lip et al. Chest 2010;137:263–72.

NICE, National Institute for Health and Care Excellence; ESC, European Society of Cardiology; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; MI, myocardial infarction; PAD, peripheral artery disease

CHA2DS2-VASc score vs Stroke risk

CHA2DS2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)
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%

CHA_2DS_2-VASc and HAS-BLED risk scoring schemes

CHA_2DS_2-VASc[1]	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65-74 years	1
Sex category (i.e. female gender)	1
Maximum score	**9**

Adapted from Lip et al. Chest 2010;137:263–72.

HAS-BLED bleeding score[1]	Score
Hypertension (SBP>160 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. Age >65 years)	1
Drugs or alcohol	1 or 2
Maximum score	**9**

Adapted from Camm et al. Eur Heart J 2010;31:2369–429.

Anticoagulation for stroke prevention in NVAF

Prescribing information for apixaban ▼ can be found at the end of this presentation

VKA therapy – overview

- Effective stroke prevention in patients with AF:[1]
  - Meta-analysis of six trials including 2,900 highly selected patients with uncertain INR control → 64% reduction in RR vs placebo
- Associated with increased risk of ischaemic stroke or intracranial bleed outside a narrow INR range:[2–4]
  - → INR <2.0: increased risk of ischaemic stroke
  - → INR >3.0: increased risk of intracranial bleed
- Associated with increased stroke risk during treatment initiation period – possibly due to hypercoagulable state:[5]
  - UK case-control study of ~71,000 newly-diagnosed AF patients → 1.71 adjusted RR in the first 30 days on warfarin vs not starting treatment

INR, international normalisation ratio; RR, relative risk

Poor INR control increases morbidity and mortality in clinical trials

- 3,587 patients randomised to warfarin (target INR 2–3) in SPORTIF III & V
- Mean follow-up (±SD) of 16.6 ± 6.3 months

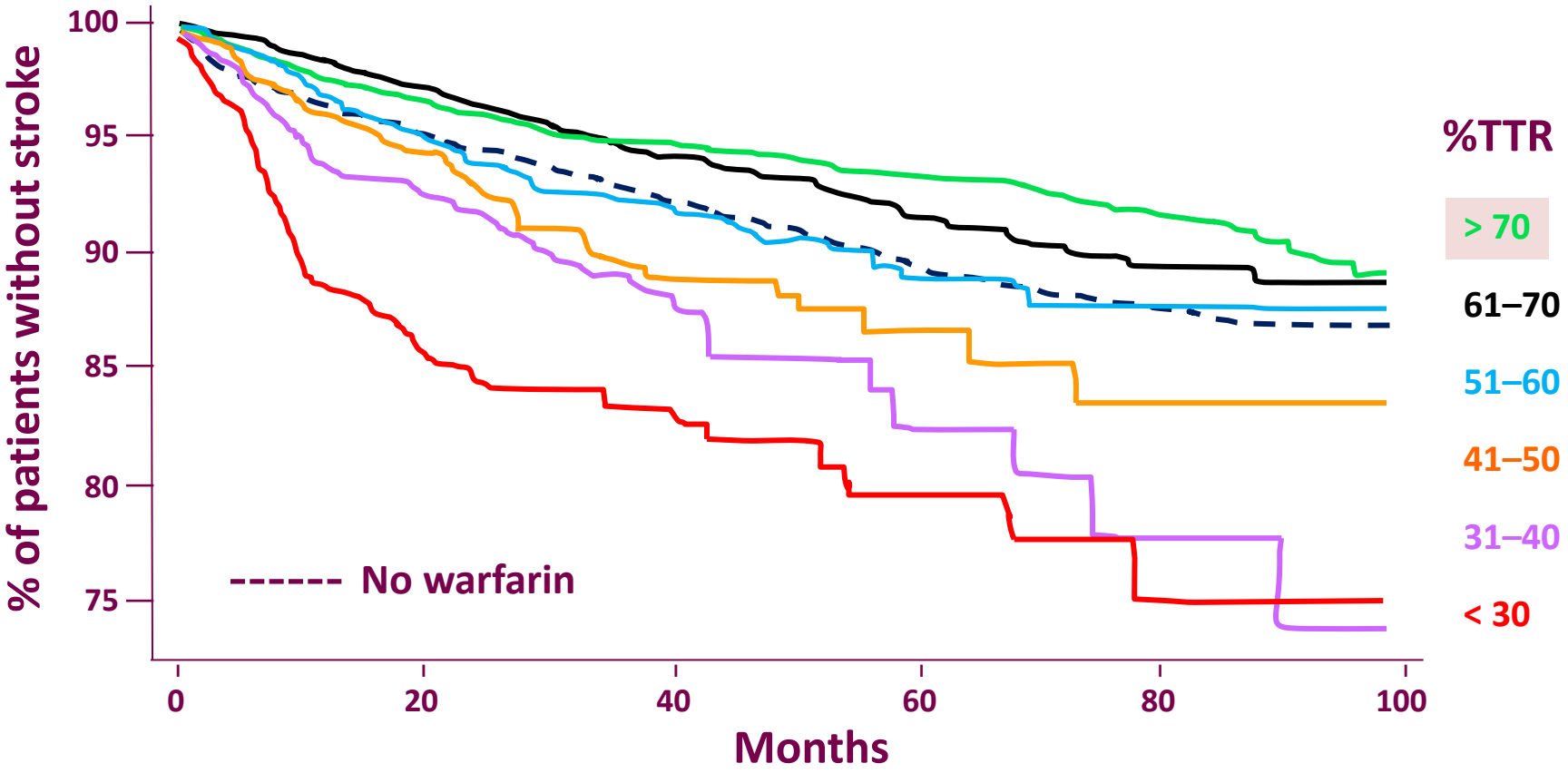
	Poor control TTR<60% n=1,190	Moderate control TTR 60–75% n=1,207	Good control TTR>75% n=1,190
# Risk Factors (%)			
1	28.5	30.1	29.1
2	30.3	29.6	35.7
>3	41.2	40.3	35.2
Mortality (%/year)	4.20	1.84	1.69
Stroke/systemic embolism (%/year)	2.10	1.34	1.07
Major bleeding* (%/year)	3.85	1.96	1.58

**Excluding haemorrhagic stroke*
Adapted from White et al. Arch Int Med 2007;167:239–45.

SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation; TTR, time in therapeutic range

Poor INR control increases the risk of stroke in real-world practice

Stroke survival in 37,907 AF patients – UK General Practice Research Database (27,458 warfarin users and 10,449 not treated with an antithrombotic)

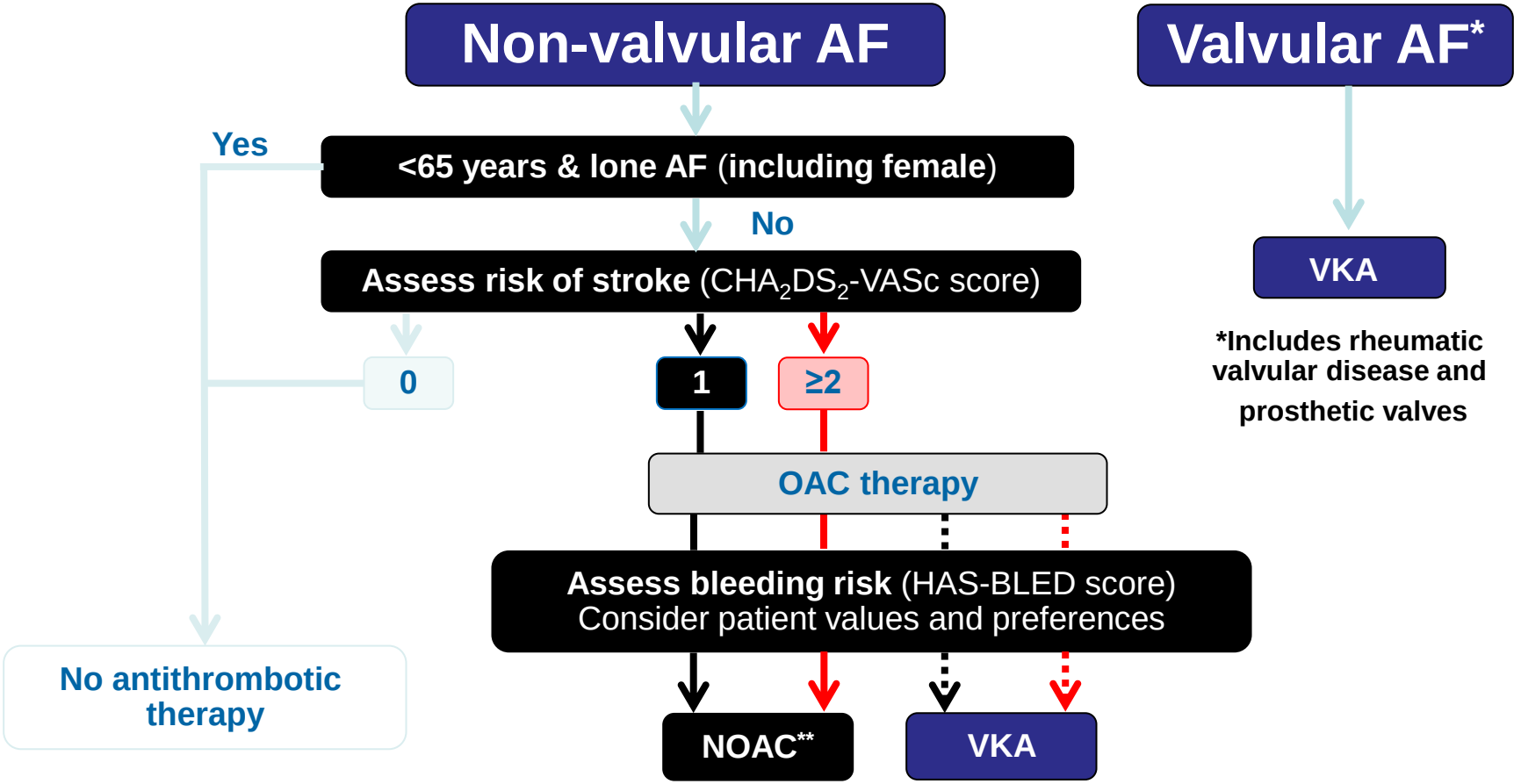


Adapted from Gallagher et al. Thromb Haemost 2011;106:968–77.

NOACs – advantages over warfarin[1–3]

- Rapid onset of action
- No significant food interactions
- Low potential for drug–drug interactions
- No requirement for routine coagulation monitoring
- BUT - Practical concerns:
  - Lack of a reversal strategy (antidote)
  - Use in older patients with renal dysfunction

ESC 2012 Recommendations: Choice of Anticoagulant



****NOACs are broadly preferable to VKA in the vast majority of patients with NVAF**

For full recommendations please refer to the ESC Guidelines for the management of atrial fibrillation (2012 update)[1]

AF: atrial fibrillation; ASA: acetyl salicylic acid; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly; INR: International Normalised Ratio; NOAC: novel oral anticoagulants; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant;
VKA: vitamin K antagonists

Adapted from Camm *et al. Eur Heart J* 2012;33:2719-47

Who to Treat - NICE CG180

- Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account [new 2014].

- Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account [new 2014].

NICE Clinical Guidance 180. 2014 http://www.nice.org.uk/guidance/cg180

How to treat – NICE CG180

- Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences. **[new 2014]**

- Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication,

How to treat – NICE CG180

- Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication

- Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation,

How to treat – NICE CG180

- The decision about whether to start treatment with NOAC should be made after an informed discussion between the clinician and the person about the risks and benefits of NOAC compared with warfarin

Local criteria for use of NOAC's over warfarin

- Allergic reaction/intolerance of coumarins
- Patients with important and unavoidable drug interactions
- Patients in whom monitoring and/or coping with variable dose regimen is difficult.

Local criteria for use of NOAC's over warfarin

- Previous significant bleed on warfarin in patients at high risk for stroke, if bleed associated with poor INR control.
- Poor INR control - e.g. more than 2 INR's >8.0 or more than 3 INR's >5.0 in 6 months
- Poor time in therapeutic range (TTR)

  i.e. less than 65%

Local criteria for use of NOAC's over warfarin

- Patients who request NOAC's as their preferred choice in terms of a **favourable lifestyle** in comparison to warfarin

NOAC Trials in AF

Randomised trials of NOACs vs warfarin in NVAF*

	RE-LY[1]	ROCKET AF[2]	ARISTOTLE[3]	ENGAGE AF-TIMI[4]
N	18,113	14,264	18,201	21,105
Design	Blinded (dabigatran) Open-label (warfarin)	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy
Treatments	▶ Dabigatran 110 mg BD† ▶ Dabigatran 150 mg BD	▶ Rivaroxaban 20 mg OD (15 mg OD in selected patients‡)	▶ Apixaban 5 mg BD (2.5 mg BD in selected patients§)	▶ Edoxaban 60 mg OD (Edoxaban 30 mg OD in selected patients)±
	▶ Warfarin (INR target: 2–3)	▶ Warfarin (INR target: 2–3)	▶ Warfarin (INR target: 2–3)	▶ Warfarin (INR target: 2–3)
Objective	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority
Inclusion criteria	Documented NVAF and >1 risk factor for stroke	Documented NVAF with moderate-to-high risk of stroke (history of stroke, TIA or SE or ≥2 risk factors)	Documented NVAF and >1 risk factor for stroke	Documented NVAF with $CHADS_2$ ≥2
Median follow-up period	2.0 years	Event-driven (590 days per-protocol; 590 days safety; 707 for ITT)	1.8 years	2.8 years

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting these findings. No conclusions about the relative efficacy or safety of any of these agents should be drawn from these data. Please refer to individual product SmPCs for further information

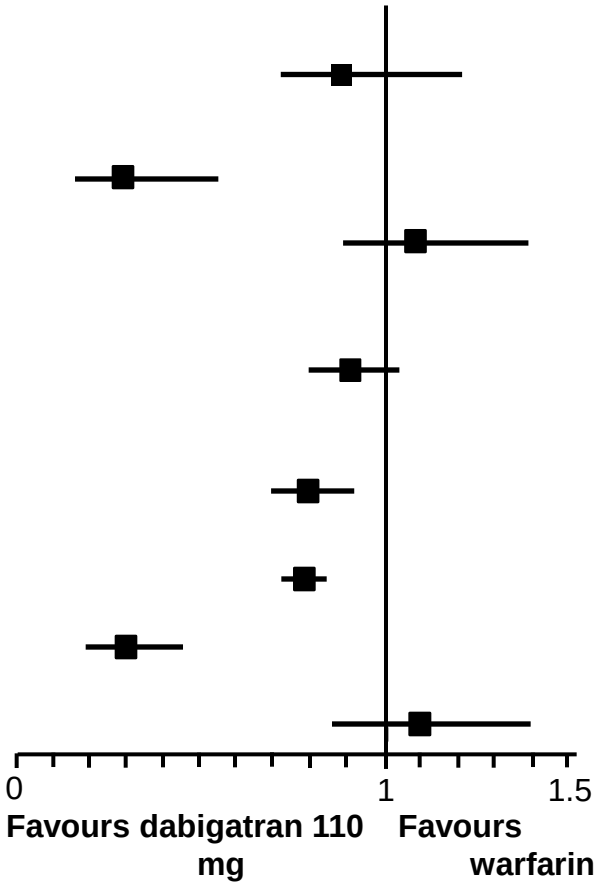
Baseline characteristics in NOACs vs warfarin trials

Data for overall study group (all study arms)	RE-LY[1,2]	ROCKET AF[3]	ARISTOTLE[4]	ENGAGE AF-TIMI 48[5,6]
Age (mean)*	72	73§	70§	72§
Gender (men)	64.0%	60.0%	65.0%	62.0%
Type of AF*				
Persistent/permanent	67.2%	81.1%	84.7%	74.6%
Paroxysmal	32.8%	17.6%	15.3%	25.4%
Newly diagnosed	–	1.0%	–	–
$CHADS_2$ score, mean*	2.1	3.5	2.1	2.8
0 or 1	31.9%	<1.0%	34.0%	–
2	35.6%	13.0 %	35.8%	77.4%
3–6	32.5%	86.5%	30.2%	22.6%
TTR in the warfarin group (mean % of the study period)	64.4%	55.0%	62.2%	64.9%

RE-LY: key efficacy and safety outcomes – dabigatran 110 mg

The RE-LY trial was a randomised trial investigating two doses of dabigatran (150 mg BD and 110 mg BD) compared with open-label use of warfarin in patients with NVAF (mean TTR of 64.4%)

	Dabigatran 110 mg (n=6,015)	Warfarin (n=6,022)	RR (95% CI)	P Value
Primary efficacy outcome				
Stroke or systemic embolism, n (%/y)[1*]	183 (1.54)	203 (1.72)	0.89 (0.73–1.09)	<0.001 For non-inferiority
– Haemorrhagic stroke, n (%/y)[2]	14 (0.12)	45 (0.38)	0.31 (0.17–0.56)	<0.001
– Ischaemic or unspecified stroke, n (%/y)[1]	159 (1.34)	144 (1.22)	1.10 (0.88–1.37)	0.42
Secondary efficacy outcome				
All-cause mortality, n (%/y)[2]	446 (3.75)	487 (4.13)	0.91 (0.80–1.03)	0.13
Safety outcomes†				
Major bleeding,‡ n (%/y)[1]	347 (2.92)	426 (3.61)	0.80 (0.70–0.93)	0.003
Major or minor bleeding, n (%/y)[3]	1754 (14.74)	2166 (18.37)	0.78 (0.73–0.83)	<0.001
Intracranial bleeding, n (%/y)[3]	27 (0.23)	90 (0.76)	0.30 (0.19–0.45)	<0.001
Major GI bleeding, n (%/y)[3]	137 (1.15)	126 (1.07)	1.08 (0.85–1.38)	0.52

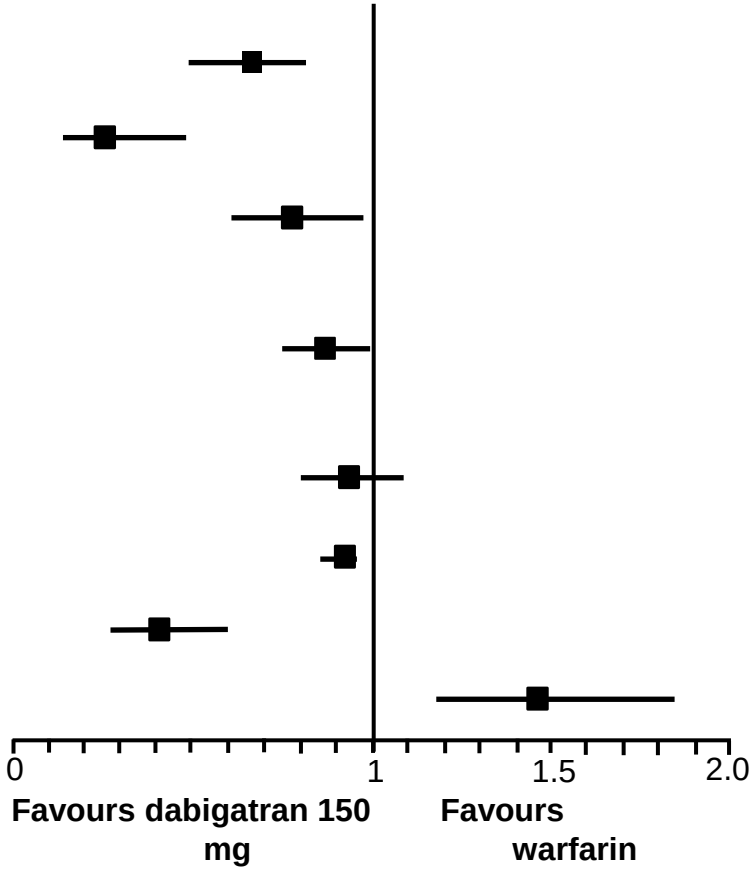


Efficacy and safety results are based on ITT population.
**Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. Haemorrhagic stroke was counted as a stroke, as was major bleeding and is part of intra-cranial bleeding.*
†The composite of major bleeding and non-major clinically relevant bleeding was not specified.
‡Primary safety outcome.
CI, confidence interval; RR, relative risk; TTR, time in therapeutic range

RE-LY: key efficacy and safety outcomes – dabigatran 150 mg

The RE-LY trial was a randomised trial investigating two doses of dabigatran (150 mg BD and 110 mg BD) in blinded manner
compared with open-label use of warfarin in patients with NVAF (mean TTR of 64.4%)

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



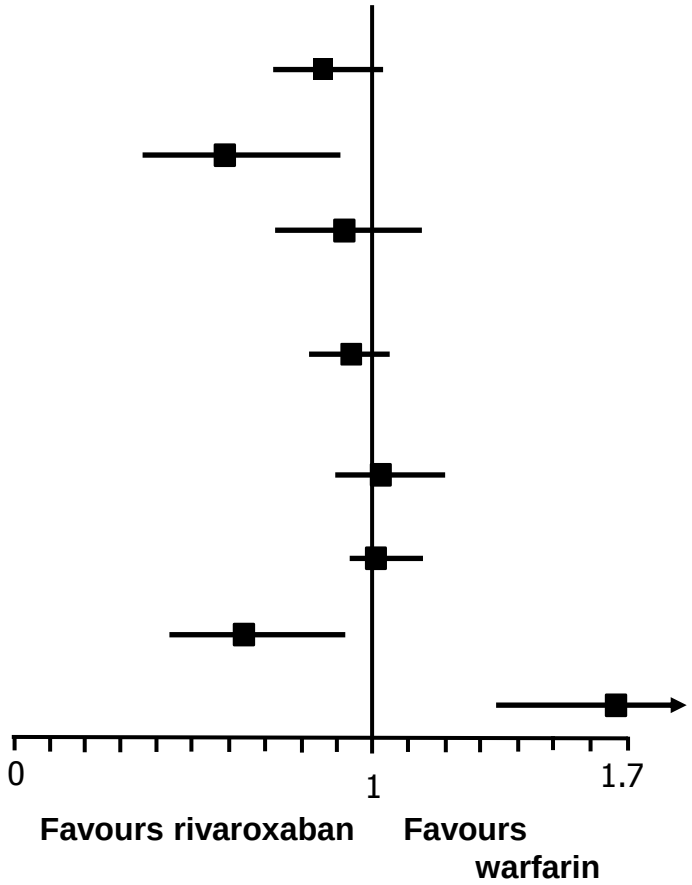
Efficacy and safety results are based on ITT population.
**Data are shown for all patients who had at least one event. All analyses were based on the time to the first event.*
P values are for superiority, unless otherwise indicated. Haemorrhagic stroke was counted as a stroke, as major bleeding and is part of intracranial bleeding.
†The composite of major bleeding and non-major clinically relevant bleeding was not specified. ‡Primary safety outcome.
CI, confidence interval; RR, relative risk; TTR, time in therapeutic range

ROCKET-AF: key efficacy and safety outcomes

The ROCKET-AF trial was a multicentre, randomised, double-blind, double-dummy, event-driven trial comparing rivaroxaban 20 mg OD (15 mg OD in selected patients) with dose-adjusted warfarin in patients with NVAF (mean TTR of 55%)

	Rivaroxaban (n=7,131)	Warfarin (n=7,133)	HR (95% CI)	P Value
Primary efficacy outcome				
Stroke or systemic embolism, n (%/y)*	269 (2.1)	306 (2.4)	0.88 (0.75–1.03)	<0.001 For non-inferiority
– Haemorrhagic stroke, n (%/y)	29 (0.26)	50 (0.44)	0.59 (0.37–0.93)	0.024
– Ischaemic stroke, n (%/y)	149 (1.34)	161 (1.42)	0.94 (0.75–1.17)	0.581
Secondary efficacy outcome				
All-cause mortality, n (%/y)†	582 (4.5)	632 (4.9)	0.92 (0.82–1.03)	0.15
Safety outcomes‡§				
Major bleeding, n (%/y)	395 (3.6)	386 (3.4)	1.04 (0.90–1.20)	0.58
Major and CRNM bleeding, n (%/y)	1475 (14.9)	1449 (14.5)	1.03 (0.96–1.11)	0.44
Intracranial bleeding, n (%/y)	55 (0.5)	84 (0.7)	0.67 (0.47–0.93)	0.02
Major GI bleeding, n (%/y)**	221 (2.0)	140 (1.24)	1.66 (1.34–2.05)	<0.0001

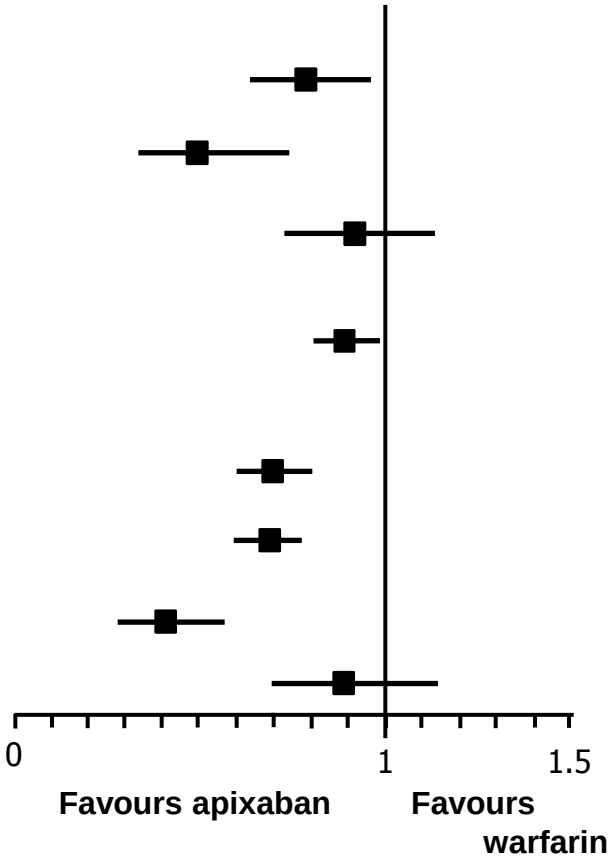
*/
†All-cause mortality data presented based on ITT population.
‡The primary safety outcome was a composite of major and non-major clinically relevant bleeding events
§The safety analysis of bleeding events was performed on the basis of the number of patients treated with rivaroxaban (7,111) or warfarin (7,125), rather than the number assigned to the treatment
**Major GI bleeding rates are the result of post-hoc analysis of data obtained during the ROCKET-AF trial[2]
CRNM, clinically relevant non-major; HR, hazard ratio; TTR, time in therapeutic range



ARISTOTLE: key efficacy and safety outcomes

The ARISTOTLE trial was a randomised, double-blind, double-dummy trial comparing apixaban 5 mg BD (2.5 mg BD in selected patients) with dose-adjusted warfarin in patients with NVAF (mean TTR of 62.2%)

	Apixaban (n=9,120)	Warfarin (n=9,081)	HR (95% CI)	P Value
Primary efficacy outcome				
Stroke or systemic embolism, n (%/y)*	212 (1.27)	265 (1.60)	0.79 (0.66–0.95)	0.01
– Haemorrhagic stroke, n (%/y)	40 (0.24)	78 (0.47)	0.51 (0.35–0.75)	<0.001
– Ischaemic stroke, n (%/y)	162 (0.97)	175 (1.05)	0.92 (0.74–1.13)	0.42
Secondary efficacy outcome				
All-cause mortality, n (%/y)†	603 (3.52)	669 (3.94)	0.89 (0.80–0.998)	0.047
Safety outcomes‡				
Major bleeding, n (%/y)§¶	327 (2.13)	462 (3.09)	0.69 (0.60–0.80)	<0.001
Major or CRNM bleeding, n (%/y)	613 (4.07)	877 (6.01)	0.68 (0.61–0.75)	<0.001
Intracranial bleeding, n (%/y)	52 (0.33)	122 (0.80)	0.42 (0.30–0.58)	<0.001
Major GI bleeding, n (%/y)	105 (0.76)	119 (0.86)	0.89 (0.70–1.15)	0.37

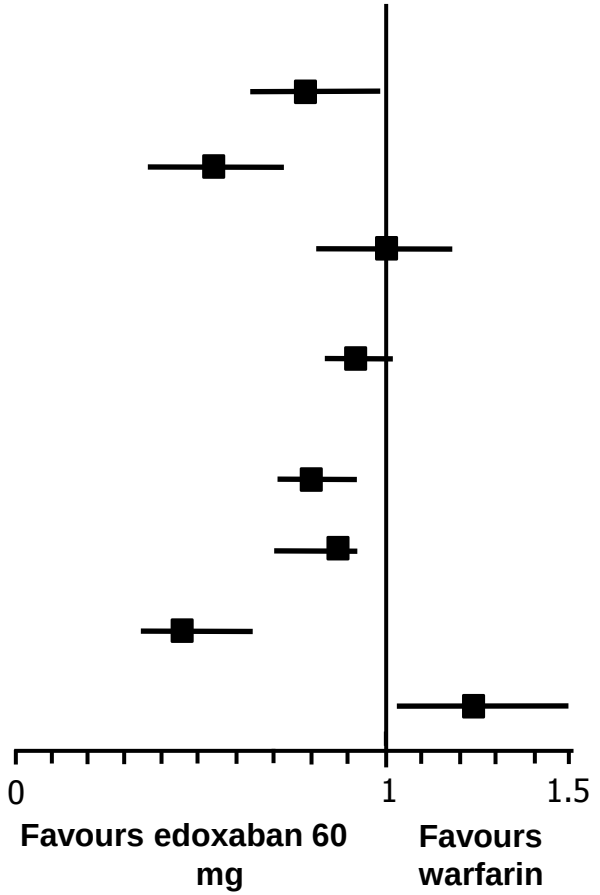


**Intention-to-treat population: follow-up continued until notification of study termination.*
†All-cause mortality data presented based on ITT population.
‡The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose.
§ The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.
¶Primary safety outcome.
CRNM, clinically relevant non-major; HR, hazard ratio; TTR, time in therapeutic range

ENGAGE AF-TIMI: key efficacy and safety outcomes

The ENGAGE AF-TIMI trial was a randomised, double-blind, double-dummy trial comparing edoxaban 60 mg OD (30 mg OD in selected patients) with warfarin in patients with NVAF (68.4% median TTR)

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



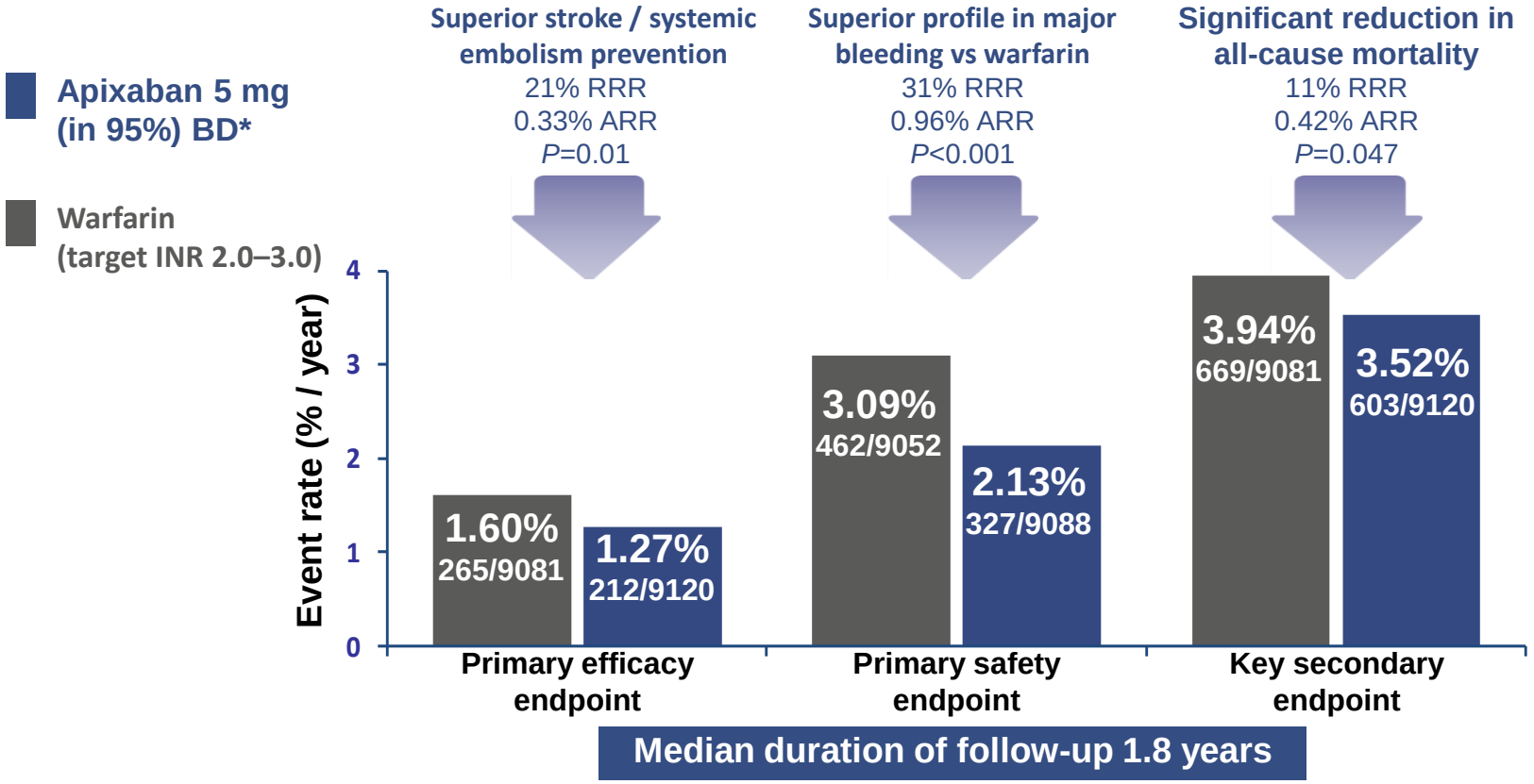
** Modified intention-to-treat population in the treatment period (excluding the open-label period that followed double-blind treatment). The analysis of the modified intention-to-treat population included data from 7,012 patients in the warfarin group and 7,012 in the edoxaban group. 97.5% confidence interval 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. For safety analysis N=7,012 for each group.

‡The primary safety outcome of major bleeding was adjudicated in accordance with the International Society on Thrombosis and Haemostasis (ISTH) criteria.

CRNM, clinically relevant non-major; HR, hazard ratio; TTR, time in therapeutic range

Apixaban is the only oral anticoagulant to demonstrate superiority vs warfarin in all of the following three outcomes



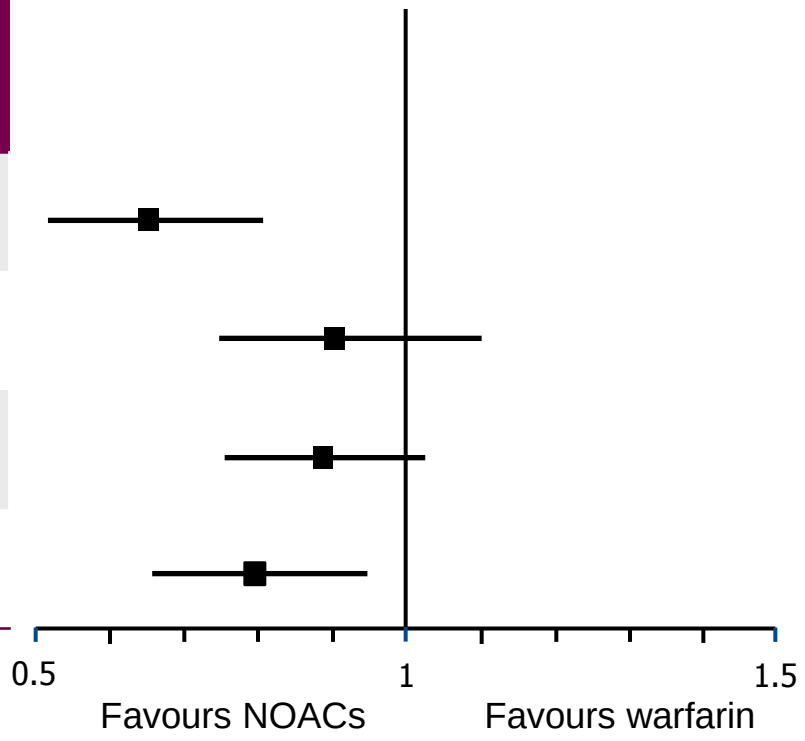
- Pre-specified hierarchical sequential testing was performed first on stroke/systemic embolism (primary efficacy endpoint) for non-inferiority, then for superiority, then on major bleeding, and finally on death from any cause (secondary endpoint)

**Patients with ≥2 of the following received a reduced dose of apixaban 2.5 mg BD: age ≥80 years, body weight ≤60 kg a serum creatinine level ≥1.5 mg/dL (133 µmol/L). Per the SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg twice daily. This additional criterion differs from the trial conduct.*

ARR, absolute risk reduction; RRR, relative risk reduction.

NOAC trials: stroke, systemic embolism vs warfarin

SSE vs warfarin (ITT population)	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150mg	1.11	1.71	0.65 (0.52–0.81)
Dabigatran 110 mg	1.54	1.71	0.90 (0.74–1.10)
Rivaroxaban	2.1	2.4	0.88 (0.75–1.03)
Apixaban	1.27	1.60	0.79 (0.66–0.95)

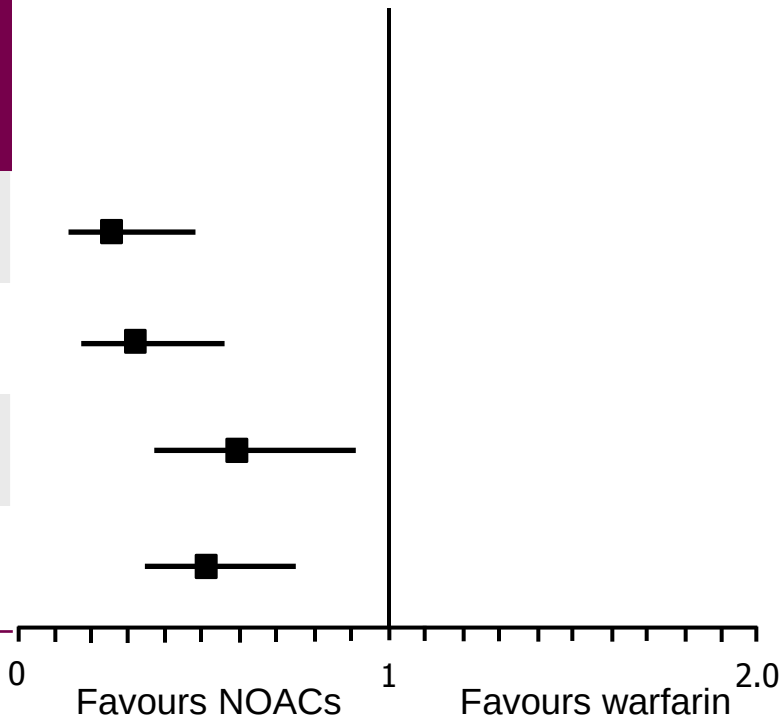


There are no head-to-head studies between these agents.

SSE, stroke and systemic embolism ; ITT, intent to treat; HR, hazard ratio; CI, confidence interval

NOAC trials: haemorrhagic stroke vs warfarin

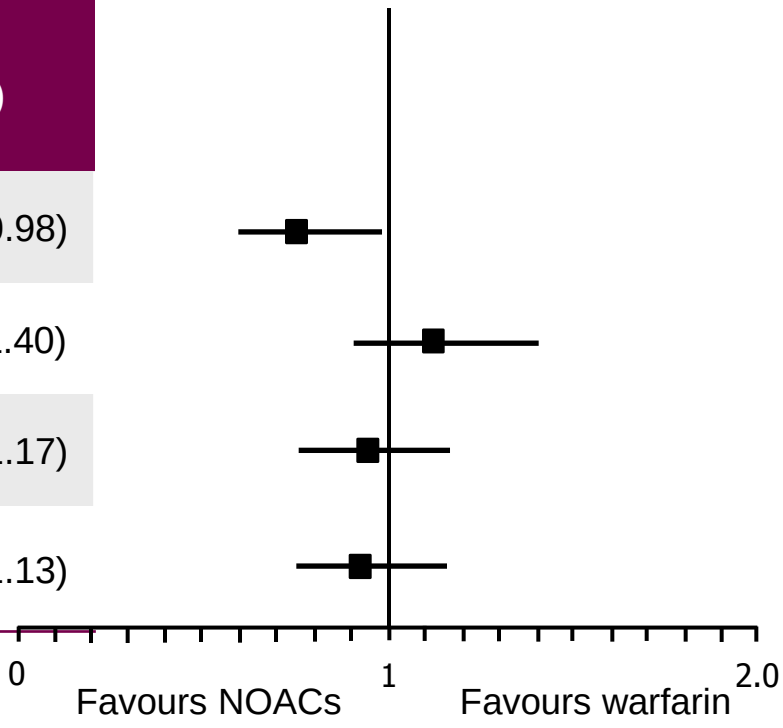
Haemorrhagic stroke vs warfarin	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150 mg	0.10	0.38	0.26 (0.14–0.49)
Dabigatran 110 mg	0.12	0.38	0.31 (0.17–0.56)
Rivaroxaban	0.26	0.44	0.59 (0.37–0.93)
Apixaban	0.24	0.47	0.51 (0.35–0.75)



There are no head-to-head studies between these agents

NOAC trials: ischaemic stroke vs warfarin

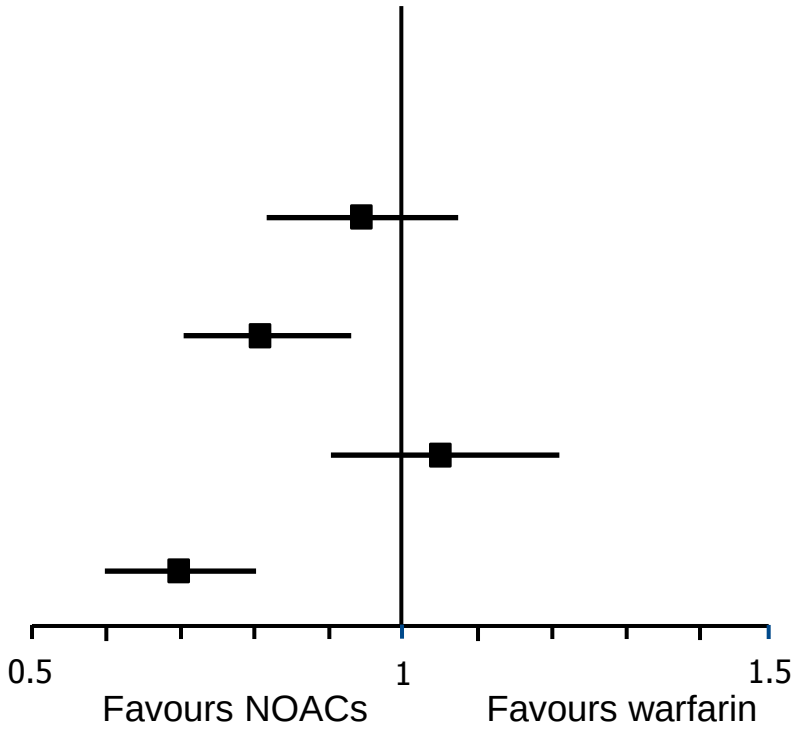
Ischaemic stroke vs warfarin	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150 mg	0.92	1.2	0.76 (0.60–0.98)
Dabigatran 110 mg	1.34	1.2	1.11 (0.89–1.40)
Rivaroxaban	1.34	1.42	0.94 (0.75–1.17)
Apixaban	0.97	1.05	0.92 (0.74–1.13)



There are no head-to-head studies between these agents

NOAC trials: major bleeding vs warfarin

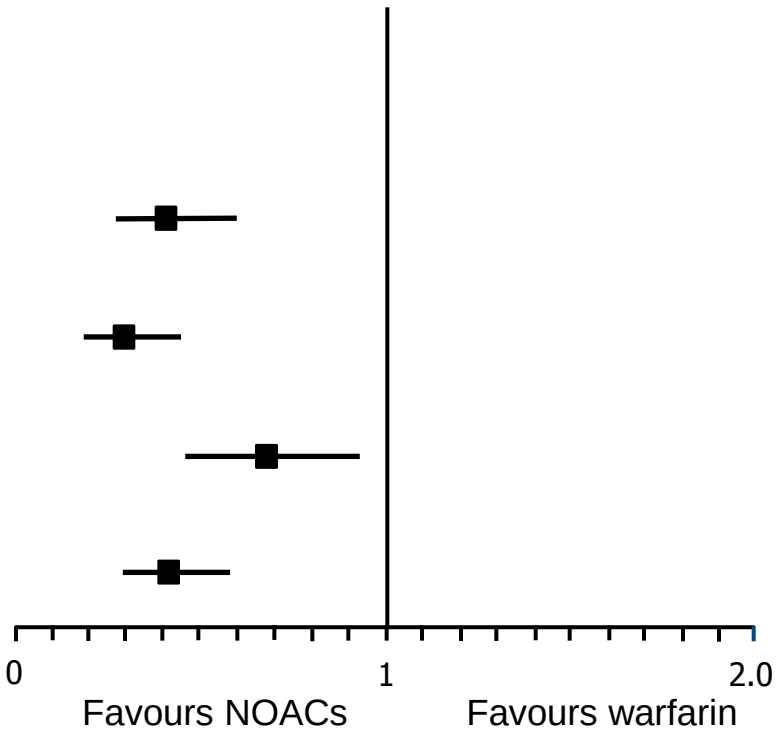
Major bleeding vs warfarin	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150mg	3.32	3.57	0.93 (0.81–1.07)
Dabigatran 110 mg	2.87	3.57	0.80 (0.70–0.93)
Rivaroxaban	3.6	3.4	1.04 (0.90–1.20
Apixaban	2.13	3.09	0.69 (0.60–0.80)



There are no head-to-head studies between these agents.

NOAC trials: intracranial bleeding vs warfarin

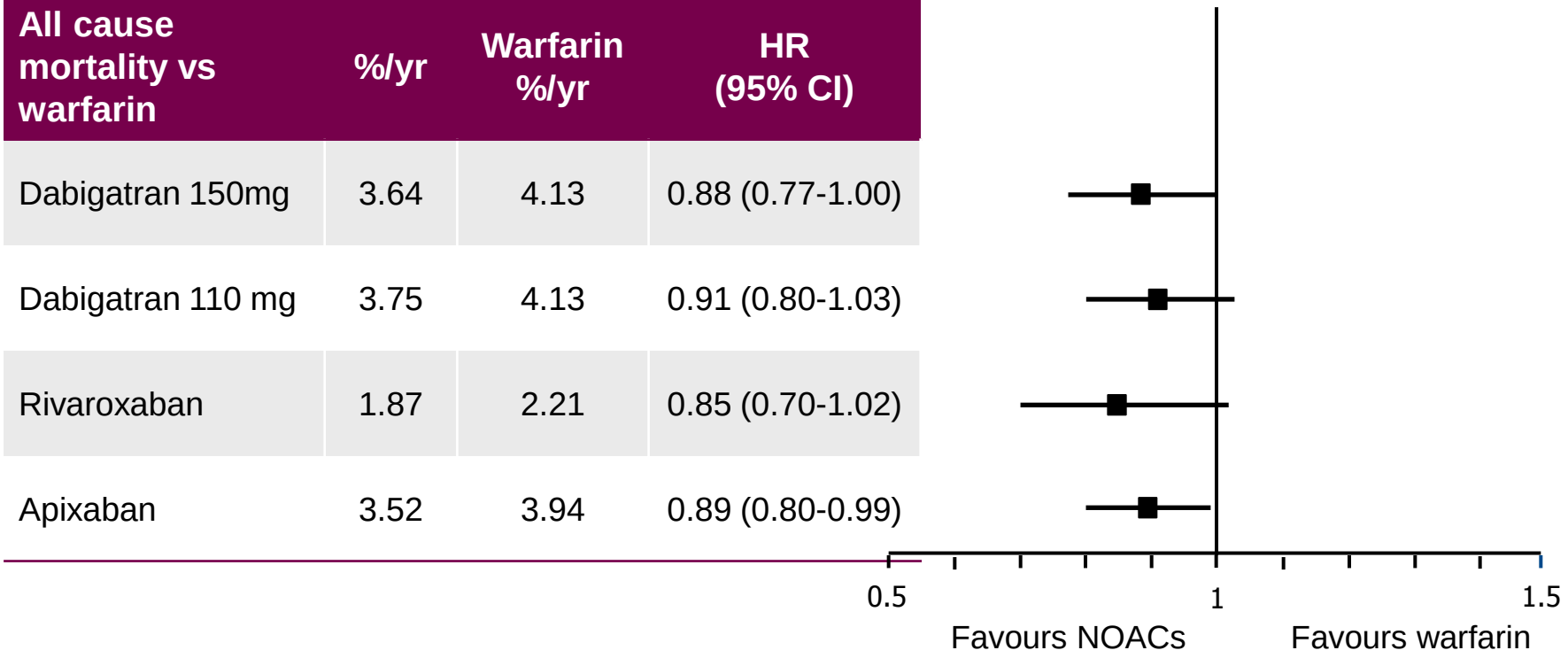
Intracranial bleeding vs warfarin	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150 mg	0.30	0.74	0.40 (0.27-0.60)
Dabigatran 110 mg	0.23	0.74	0.31 (0.20-0.47)
Rivaroxaban	0.5	0.7	0.67 (0.47-0.93)
Apixaban	0.33	0.80	0.42 (0.30-0.58)



There are no head-to-head studies between these agents

NOAC trials: all cause mortality vs warfarin

All cause mortality vs warfarin	%/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150mg	3.64	4.13	0.88 (0.77-1.00)
Dabigatran 110 mg	3.75	4.13	0.91 (0.80-1.03)
Rivaroxaban	1.87	2.21	0.85 (0.70-1.02)
Apixaban	3.52	3.94	0.89 (0.80-0.99)

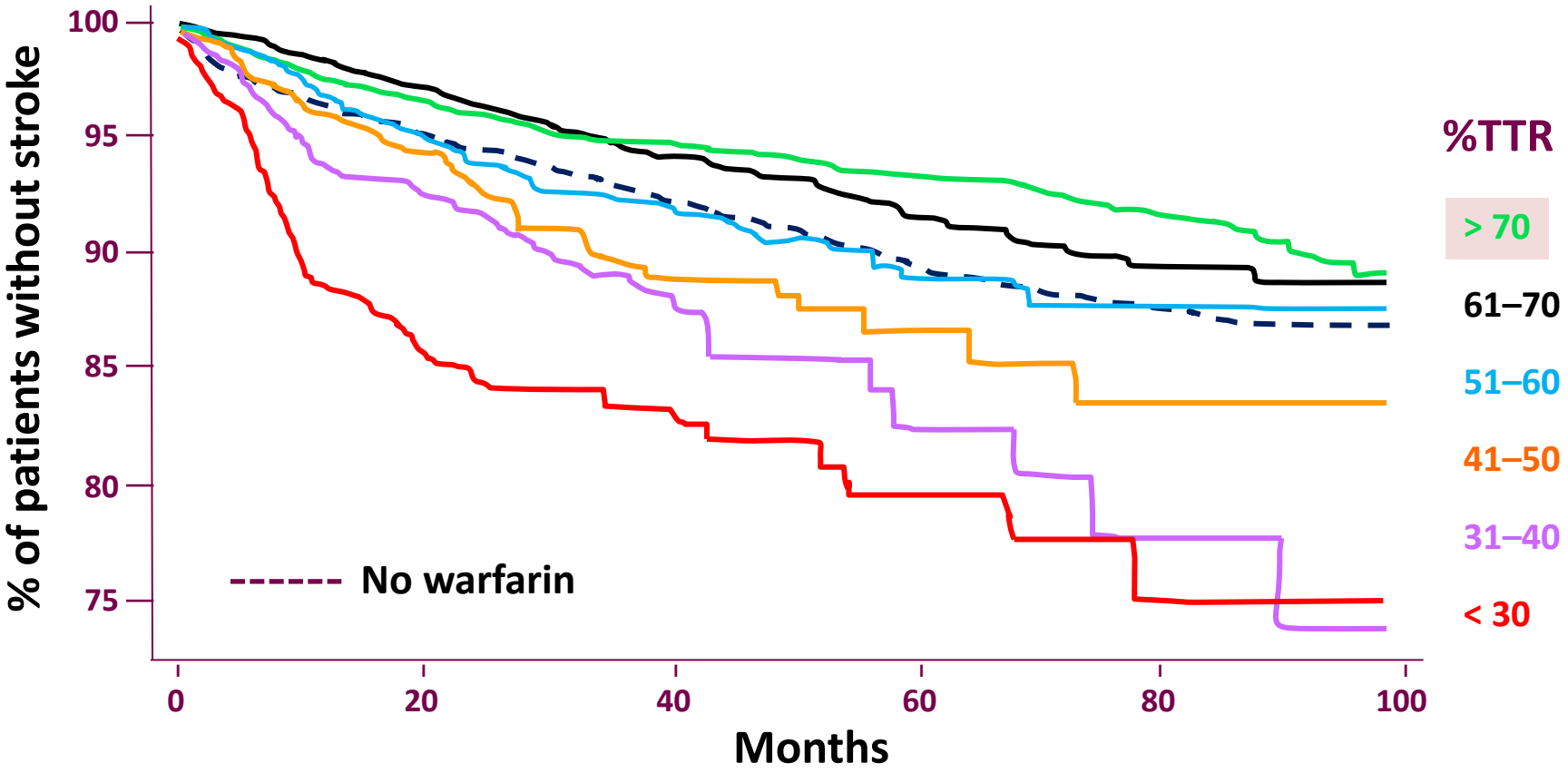


There are no head-to-head studies between these agents

1. Connolly SJ et al. N Engl J Med 2009;361:1139–1151;
2. Patel MR et al. NEJM 2011;365:883–891 and Supplementary Appendix

Poor INR control increases the risk of stroke in real-world practice

Stroke survival in 37,907 AF patients – UK General Practice Research Database (27,458 warfarin users and 10,449 not treated with an antithrombotic)



Adapted from Gallagher et al. Thromb Haemost 2011;106:968–77.

Which NOAC's do I use in SPAF

- Once daily preparation preferred: rivaroxaban or edoxaban
- Light (<60kg) elderly patients with mild renal impairment: apixaban 2.5 mg bd.
- Patient has medication supplied in blister packs: use rivaroxaban, apixaban, edoxaban
- Mild bleeding PR e.g from haemorrhoids: use apixaban with care
- High risk of recurrent CVA - Use Dabigatran

Decision making pointers: Which NOAC don't I use?

Dabigatran: Avoid in:

- Patients who would find o.d. dose better
- Patients using blister packs
- Patients on verapamil
- Patients with dyspepsia
- Creat clearance <60mls/min

Apixaban: Avoid in

- Patients who would find o.d. dose better

Safety and anticoagulation

Reversal or anticoagulation

PATIENT RECEIVING RIVAROXABAN THERAPY: HAEMORRHAGE PROTOCOL

STOP: RIVAROXABAN

Contact Haematologist

Request: 1. Coagulation screen to include PT (INR), APTT (consider thrombin time)
[Important to document time of last dose of RIVAROXABAN]
2. Full blood count and renal function / eGFR

PT (and TT) normal

NO Rivaroxaban anticoagulant effect likely to be present

PT (and TT) prolonged

Rivaroxaban anticoagulant effect maybe present (consider oral charcoal if Rivaroxaban ingestion < 2 hours)

MILD BLEED

MAJOR BLEED

LIFE THREATENING BLEED

- Mechanical compression
- Tranexamic Acid
  - oral 25 mg/kg
  - i.v. 15 mg/kg
- Delay next Rivaroxaban dose or discontinue treatment

Continues to bleed

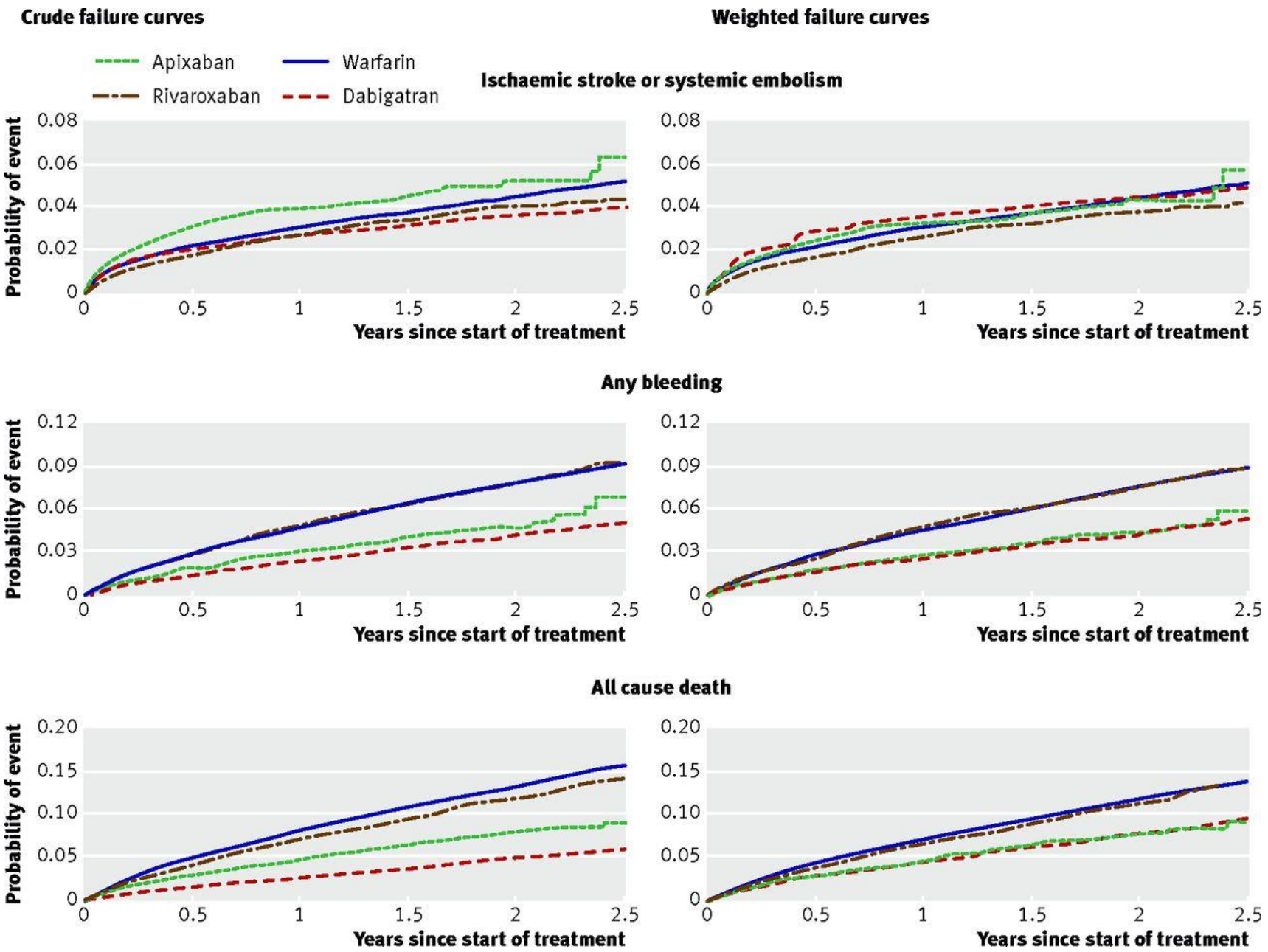
Maintain BP and Urine Output

- Optimise tissue oxygenation
- Control haemorrhage
  - Compression
  - Surgical intervention
- Tranexamic Acid (25 mg/kg i.v.)
- Red Cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10^9/l or
  - If CNS bleed aim Plt > 100 x 10^9/l

Prothrombin Complex Concentrate (PCC)
- Beriplex 35 - 50 U/kg or
- Octaplex 40 U/kg (max 3000 U in one dose)

Major Bleed: Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome

Larsen BMJ June 2016



Variables I year FU	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†
Ischaemic stroke or systemic embolism	210	4.86	3.92	327	2.77	3.73	161	3.04	2.89	1004	3.28	3.25
Ischaemic stroke	204	4.71	3.72	321	2.72	3.68	156	2.95	2.79	920	3.00	3.01
All cause mortality	232	5.23	5.01	319	2.66	4.62	413	7.69	7.02	2652	8.52	7.41
Ischaemic stroke, systemic embolism, or death	424	9.81	8.71	623	5.28	7.92	537	10.15	9.38	3483	11.39	10.28
Any bleeding	121	3.78	3.13	253	2.77	2.85	186	5.57	4.83	959	5.53	4.71
Major bleeding	90	2.80	2.29	203	2.22	2.04	149	4.44	3.92	725	4.16	3.58
Intracranial bleeding	15	0.46	0.40	19	0.21	0.22	14	0.41	0.31	118	0.66	0.55
2.5 years' follow-up:												
Ischaemic stroke or systemic embolism	225	4.08	3.32	441	1.84	2.32	201	2.34	2.21	1447	2.39	2.33
Ischaemic stroke	219	3.97	3.17	427	1.78	2.26	196	2.28	2.15	1337	2.20	2.17
All cause mortality	274	4.82	4.69	600	2.44	4.04	592	6.74	6.31	4469	7.17	6.20
Ischaemic stroke, systemic embolism, or death	473	8.58	7.75	992	4.13	6.10	733	8.53	8.03	5524	9.11	8.13
Any bleeding	143	3.52	2.90	461	2.48	2.67	252	4.60	4.09	1579	4.60	3.93
Major bleeding	109	2.67	2.15	376	2.01	2.02	200	3.63	3.27	1198	3.46	2.98
Intracranial bleeding	18	0.43	0.41	35	0.18	0.17	23	0.40	0.31	190	0.53	0.44

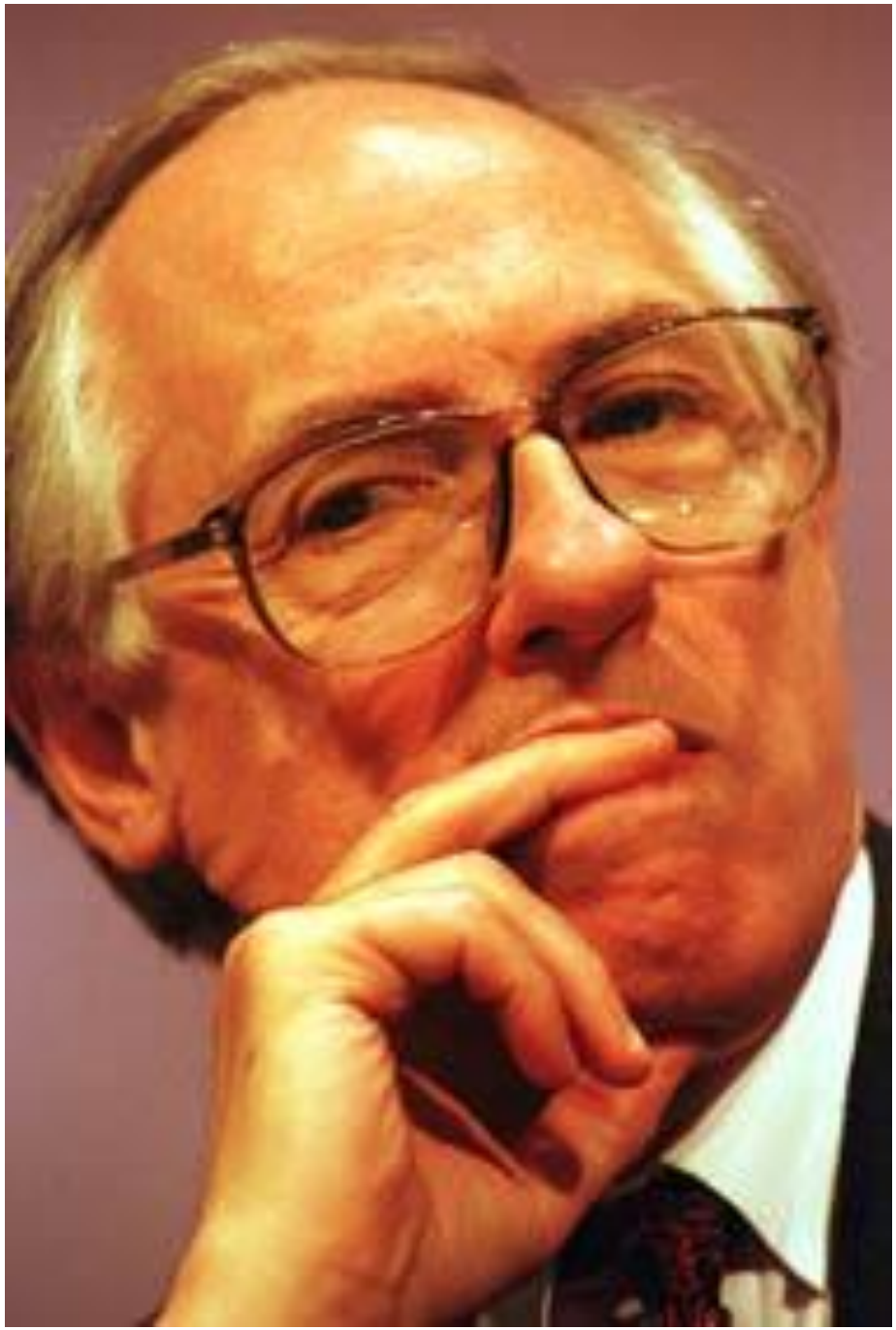
Major bleeding in warfarin patients

- PCC use in Good Hope 2014
- 55 patients received PCC
- 52 pts on warfarin 3 pts on rivaroxaban
- 14/52 died (26.9%)
- similar to previous audits: 2011 - 30%; 2012 - 39%; 2013 - 19.8%.
- consistently higher than international average of 10.6%[1].

Case report

- **63 year old man**
- **Busy active professional and family life with travel and entertaining**
- **Aortic valve replacement 2 years earlier**
- **Warfarin for AVR and AF**
- **Poor control of INR**

- Slipped and fell on front steps of his house
- Head injury ± ?CVA
- INR > 6
- Massive intra-cranial haemorrhage
- Pronounced dead 24hrs later



Idarucizumab - Praxbind

- humanized monoclonal antibody fragment (Fab)
- indicated for reversal of Dabigatran
- Three randomized, placebo-controlled studies were conducted in a total of 283 healthy volunteers
  - 224 received at least one dose of PRAXBIND
  - 30 subjects were aged 65 years or older (median age=36 years)
- 12 subjects had mild renal impairment and 6 had moderate impairment†

Results

- Immediately after 5 g PRAXBIND

- dabigatran plasma concentrations were reduced to below the lower limit of quantification
- coagulation paramaters (dTT, ECT, aPTT, TT, ACT) returned to baseline levels
- Reduction in dabigatran was observed ≥24 hrs
- In some patients, re-distribution of dabigatran led to re-elevation of dTT, ECT, aPTT, and TT

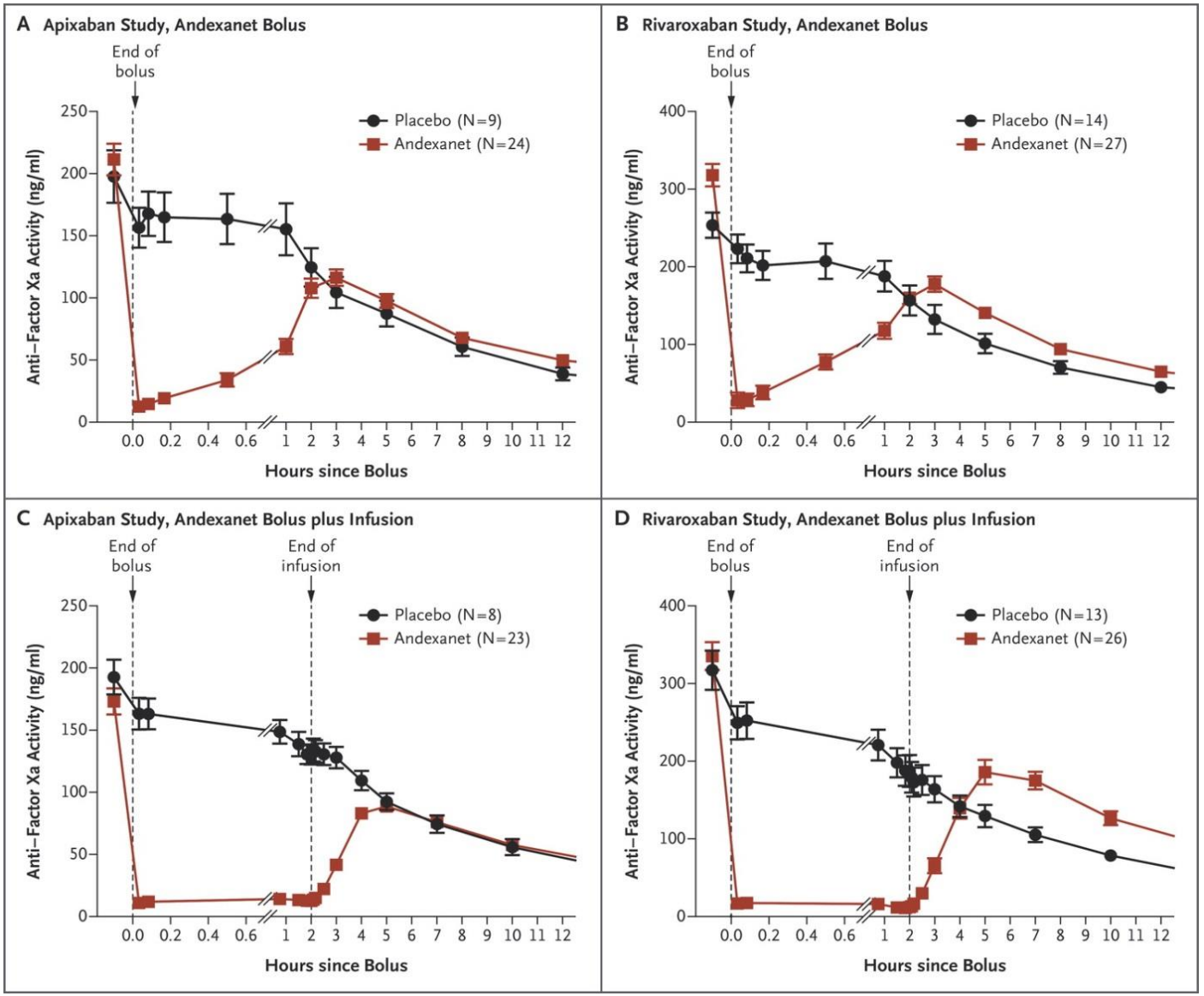
Adexanet alfa

- Modified human Factor Xa decoy protein
- Binds all factor X inhibitors - high affinity

- Reverses apixaban and rivaroxaban levels

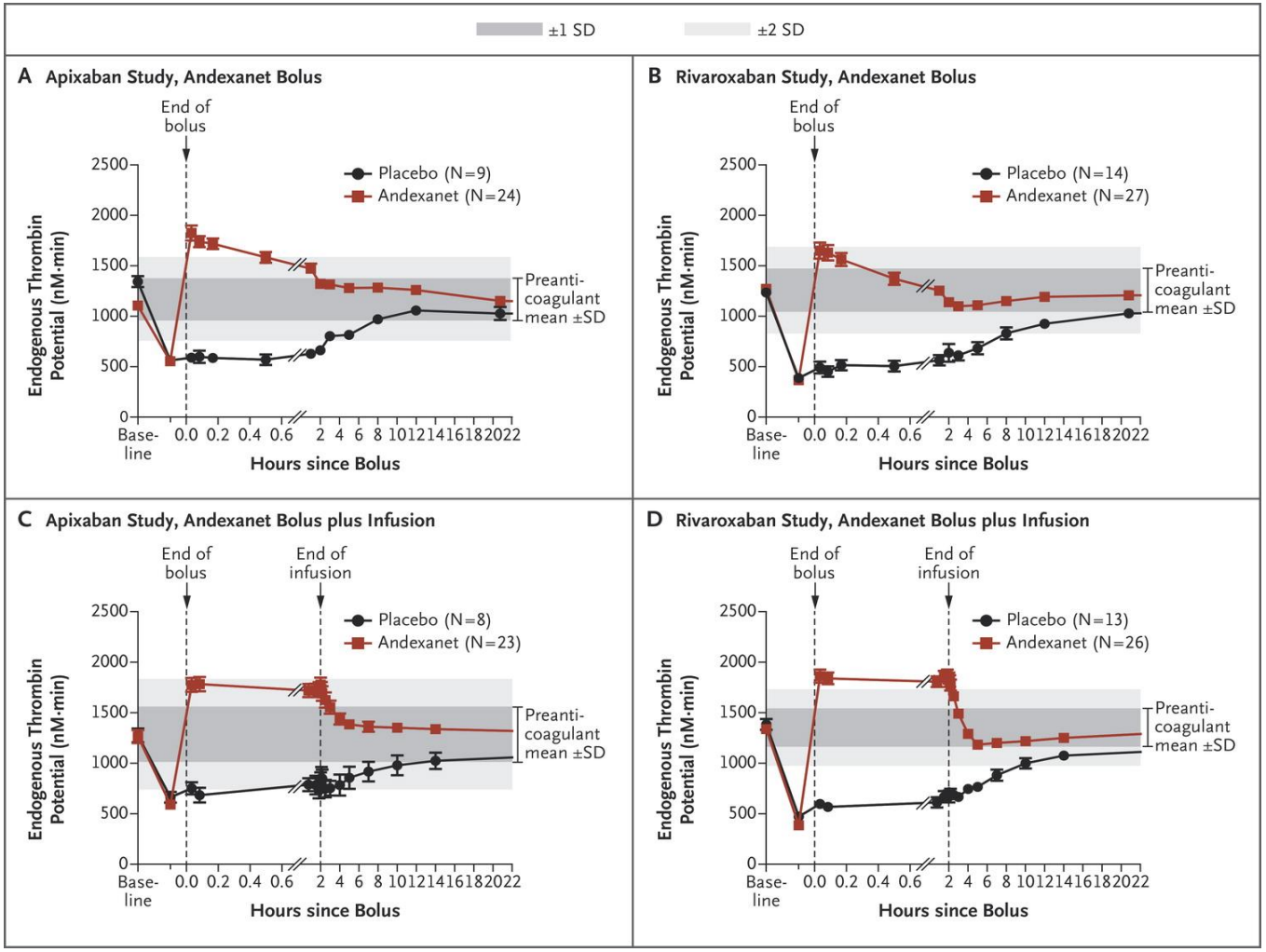
- Reduces anti-Fxa levels
- Restores Thrombin generation (100% vs 11%)

Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.



Siegal DM et al. N Engl J Med 2015;373:2413-2424.

Time Courses of Thrombin Generation before and after the Administration of Andexanet.



Siegal DM et al. N Engl J Med 2015;373:2413-2424.

‘But you can reverse warfarin’

- Antidotes for Warfarin
- Vitamin K
- Prothrombin Complex Concentrate (PCC)

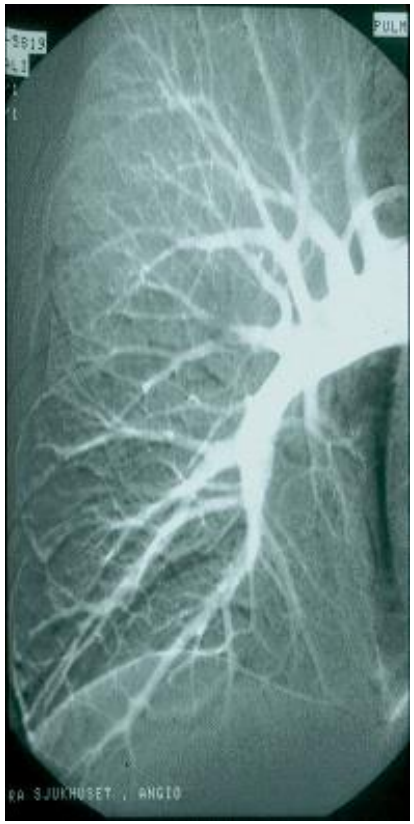
Major bleeding in warfarin patients

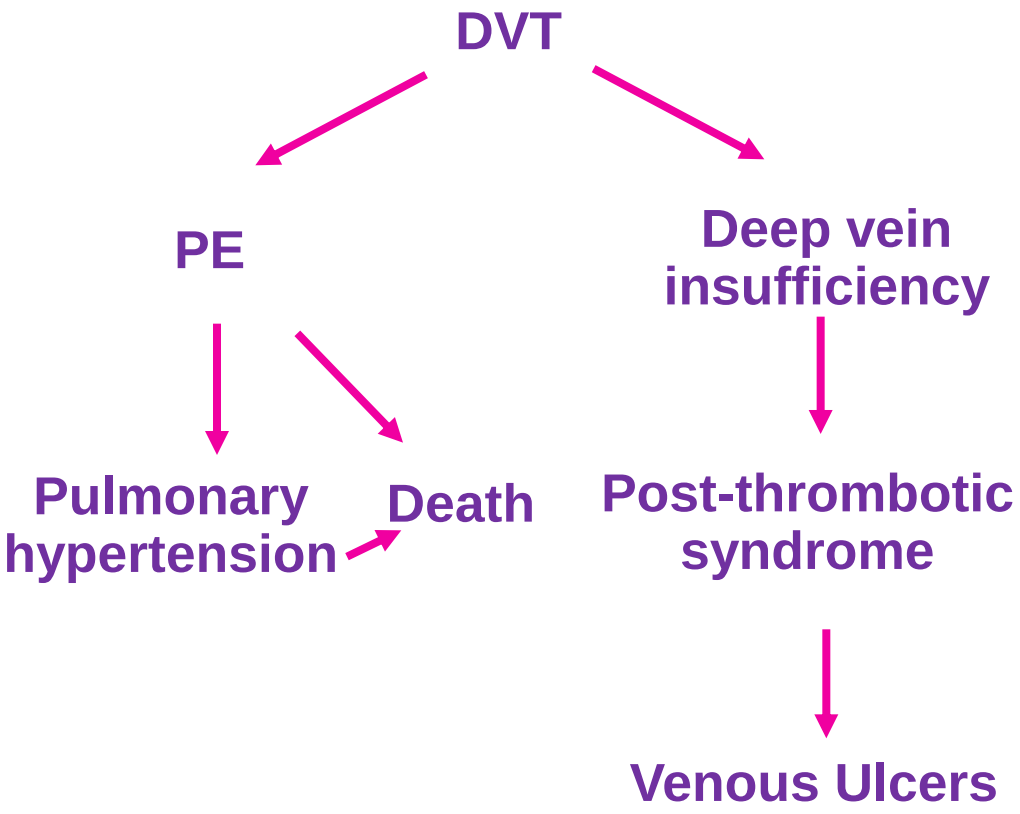
- Review of PCC use in Good Hope 2014
- 55 patients received PCC
- 52 pts on warfarin 3 pts on rivaroxaban
- 14/52 died (26.9%)
- similar to previous audits: 2011 - 30% died; 2012 - 39% died; 2013 - 19.8% died.
- consistently higher than international average of 10.6%[1].

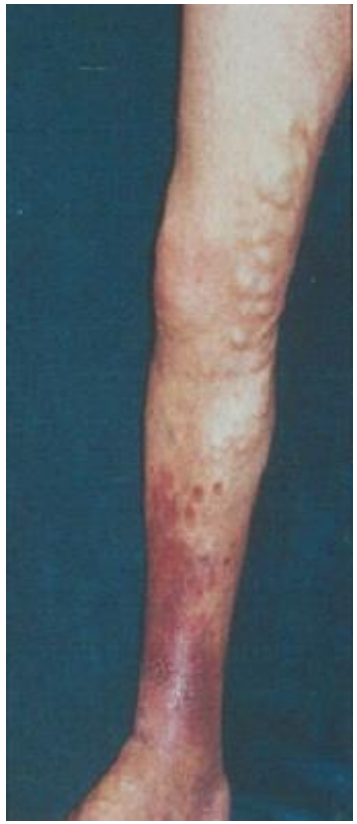
Warfarin / Heparin - Adverse effects

- 600 negligence claims related to use of anticoagulants, in the UK 1990- 2002.
- 120 cases had resulted in death
- Most frequent errors were:
- overdose,
- poor record keeping,
- contraindications for use
- problems with monitoring

Venous thromboembolism (VTE)

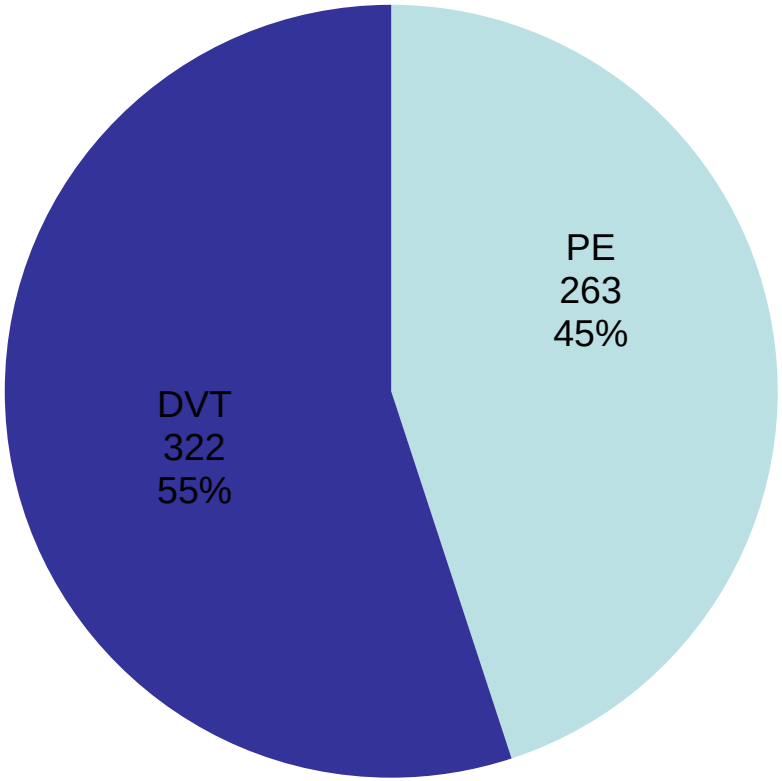




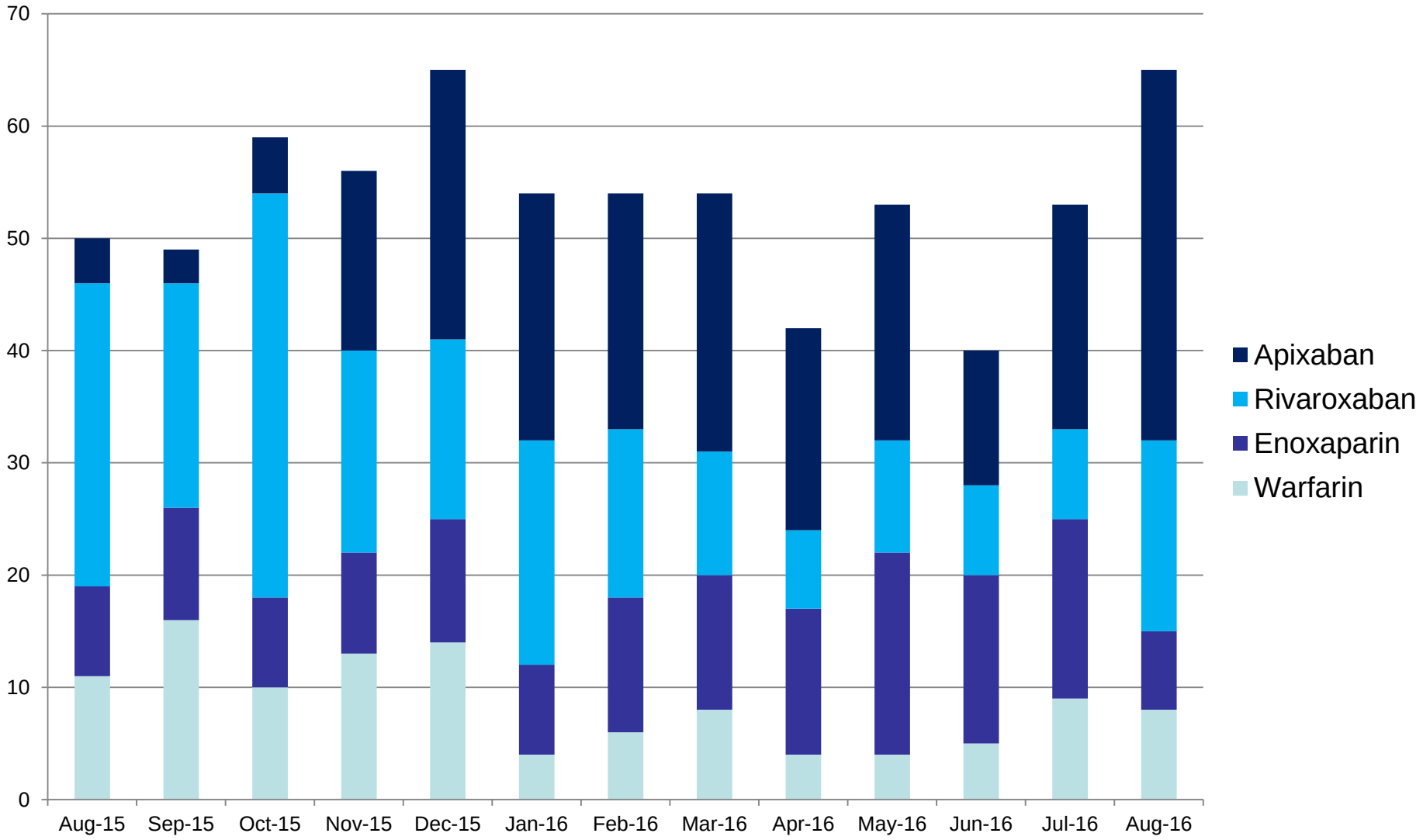


Crude mortality 15-20% within 3 months of diagnosis

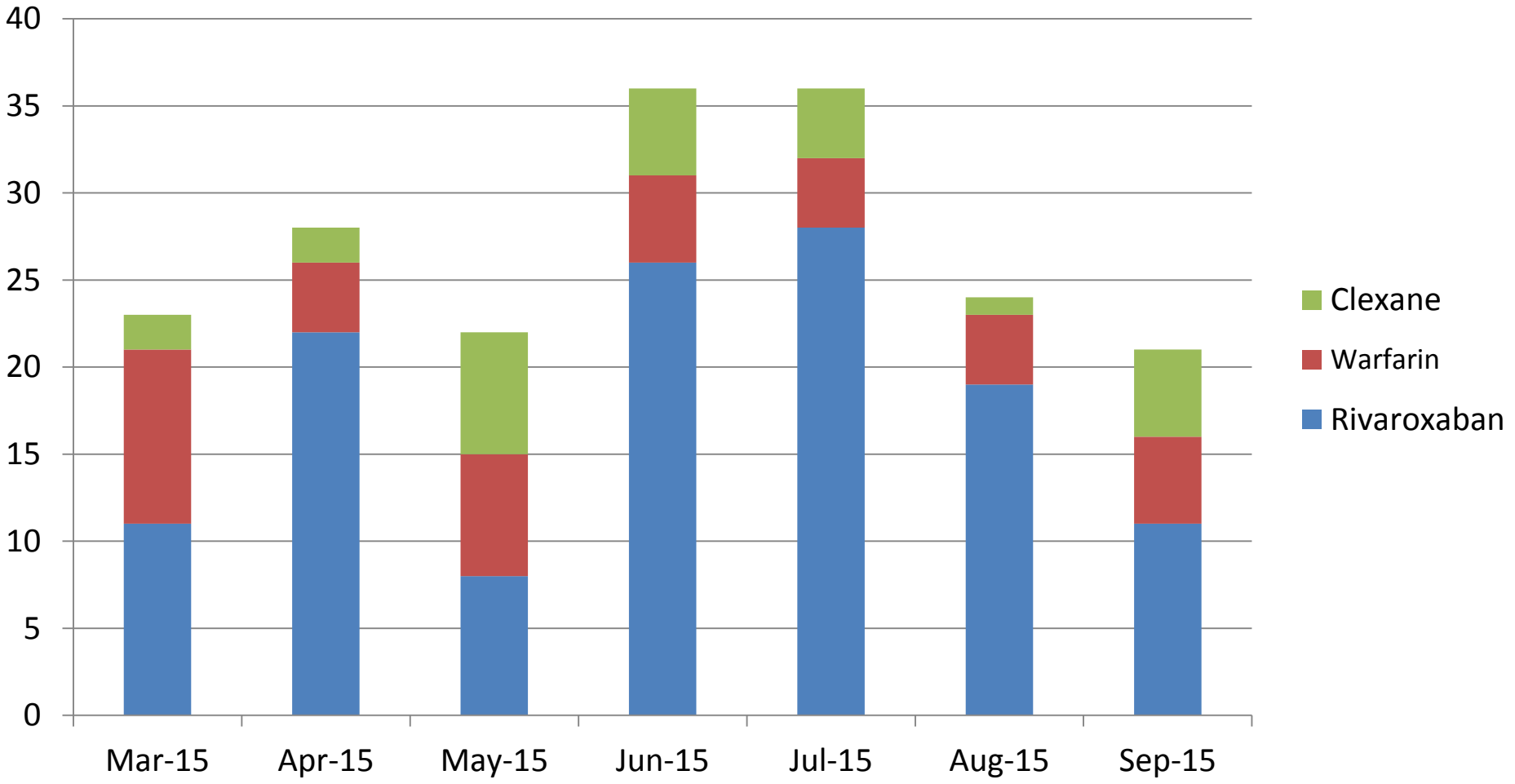
Total VTE's HEFT (FY 2014-2015)



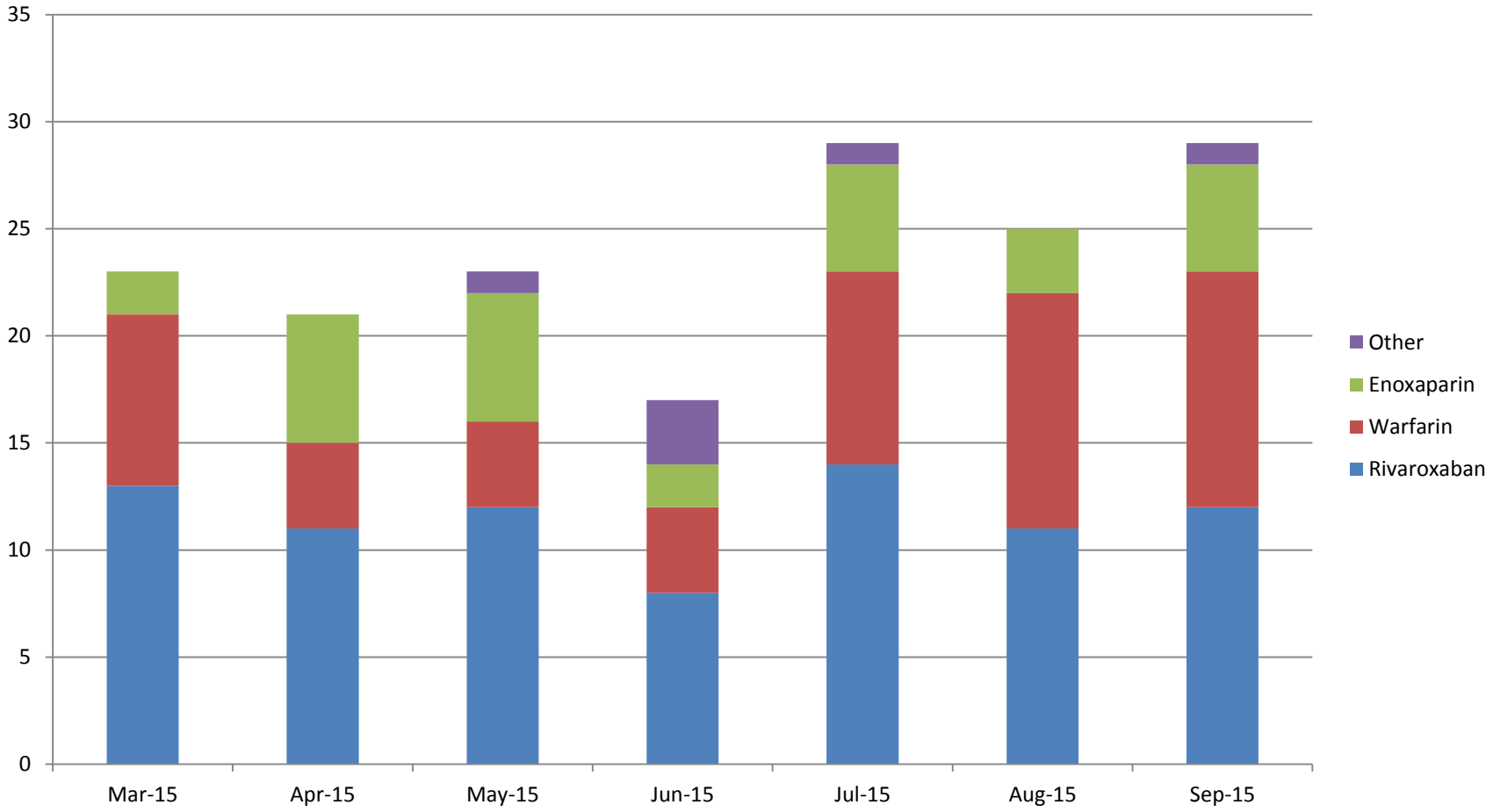
VTE treatment type 2015-16 - HEFT

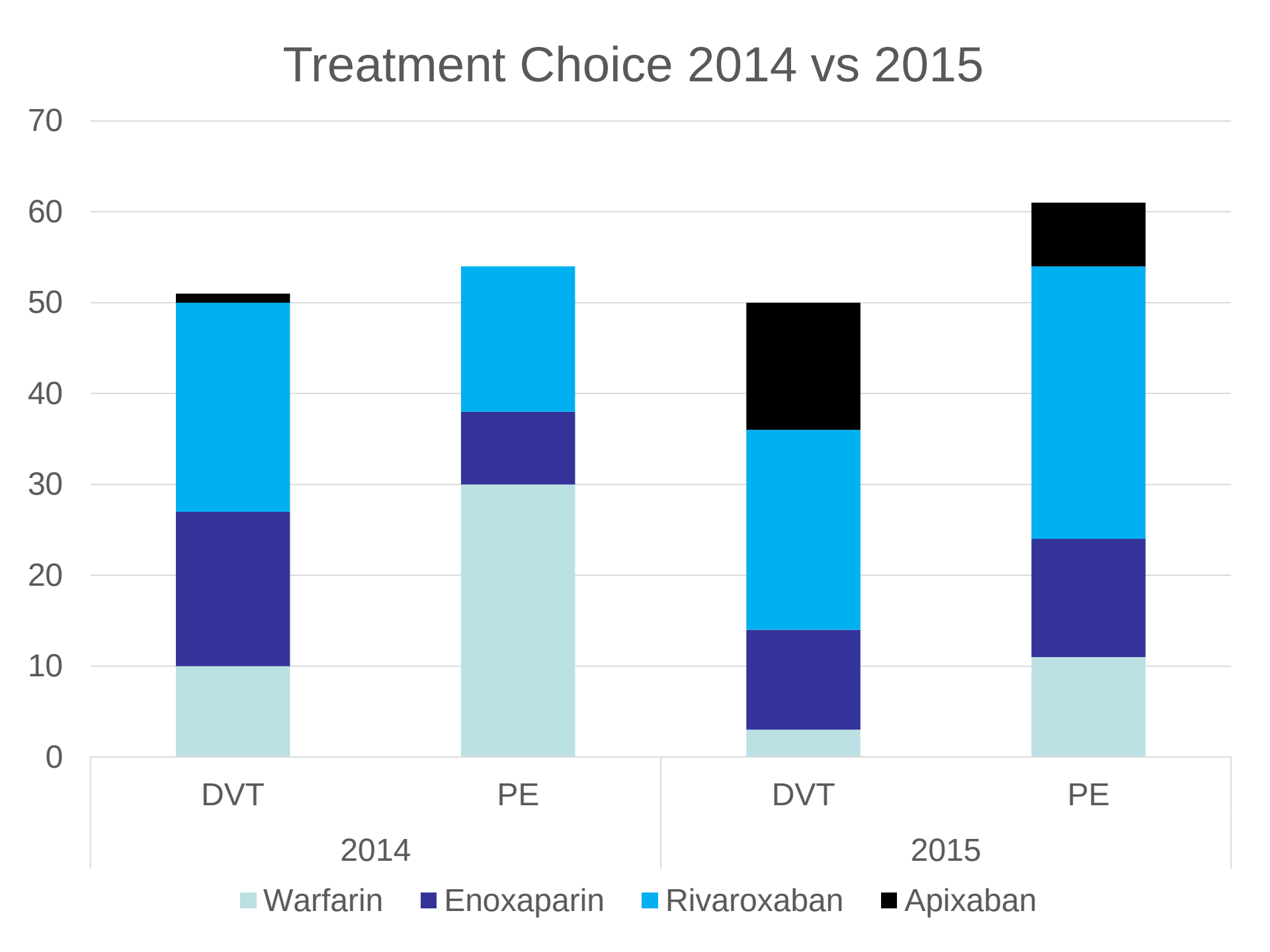


DVT Treatment type

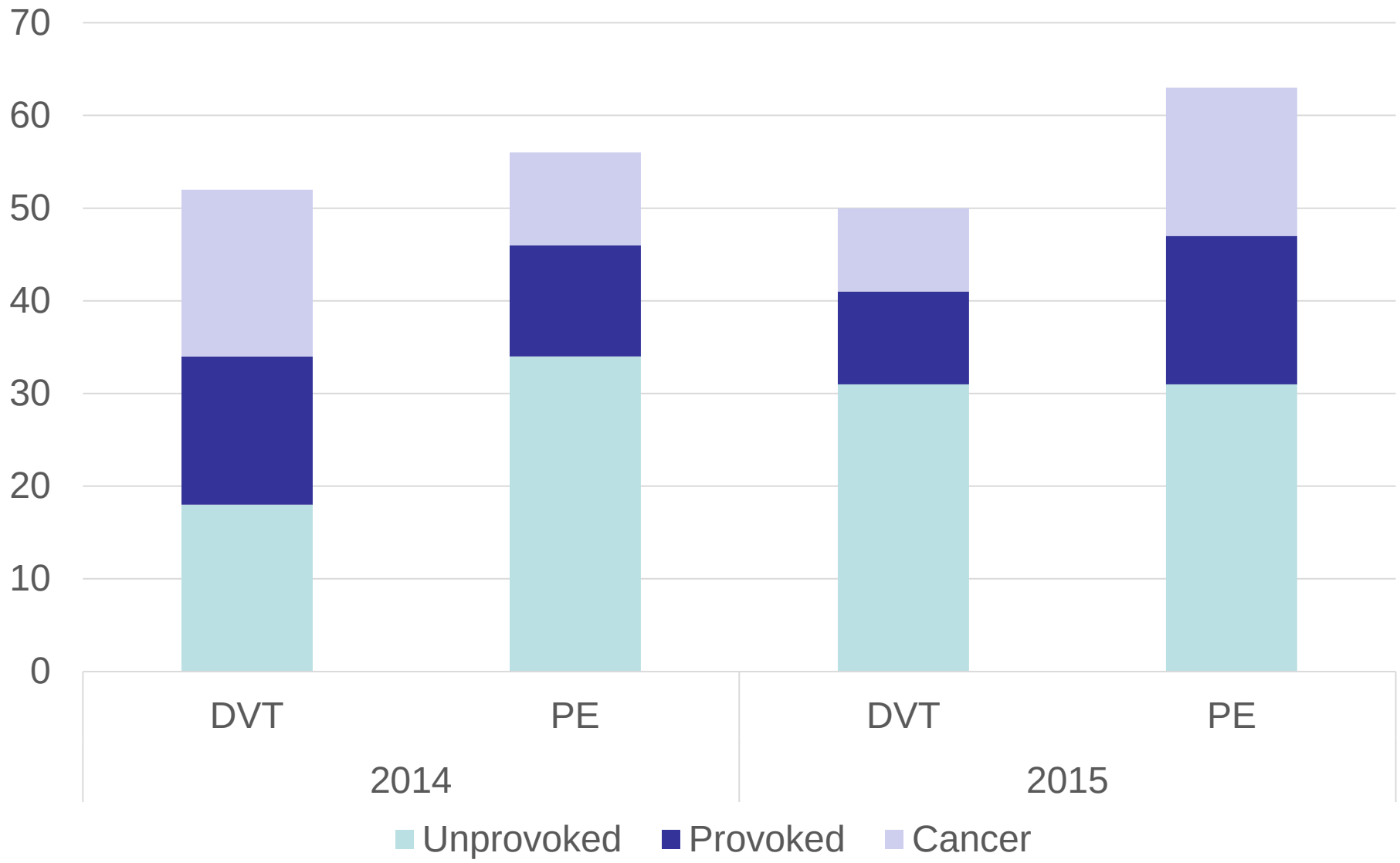


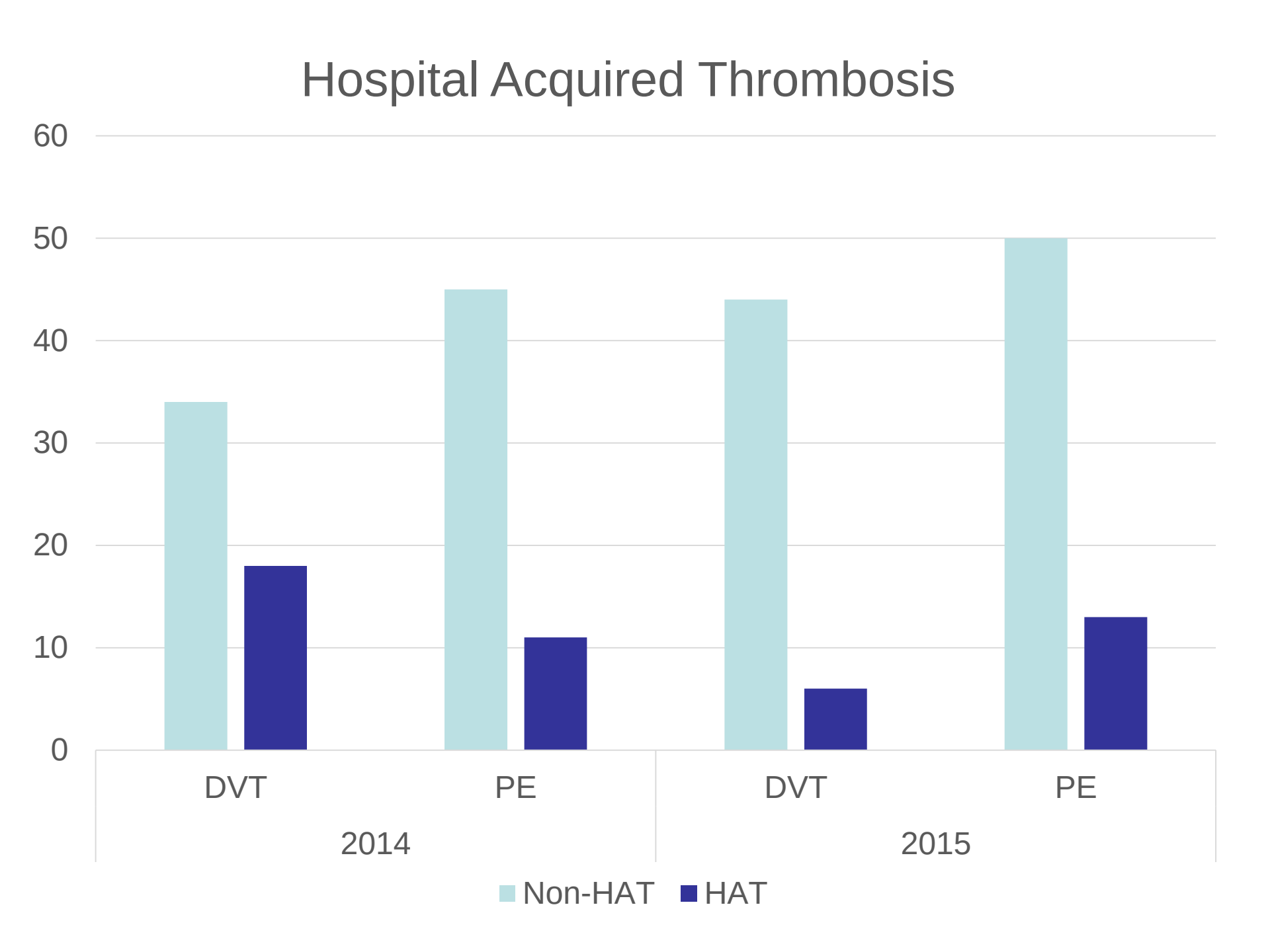
PE Treatment Type

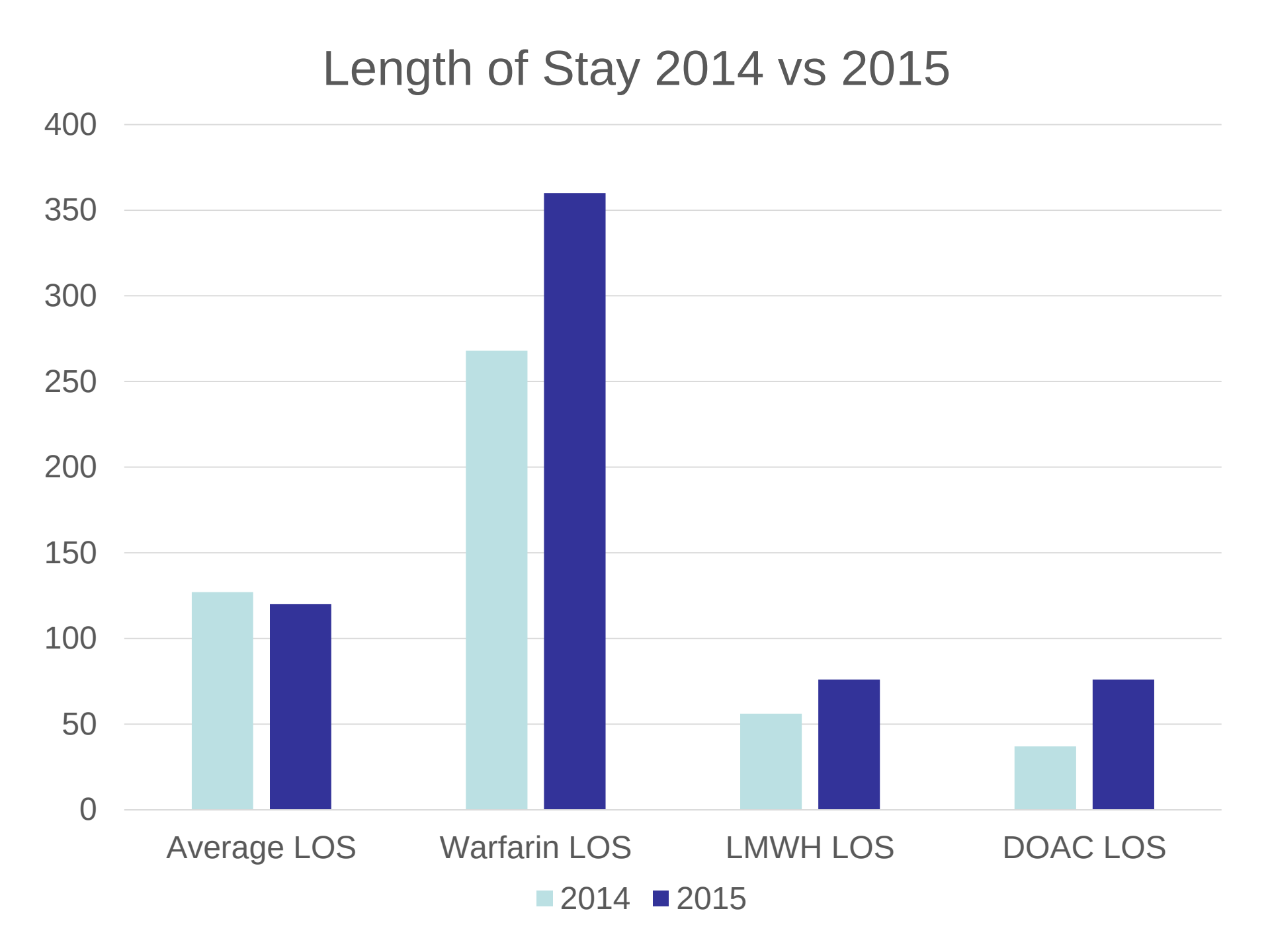



Treatment Choice 2014 vs 2015
70
60
50
40
30
20
10
0
DVT
PE
DVT
PE
2014
2015
Warfarin
Enoxaparin
Rivaroxaban
Apixaban

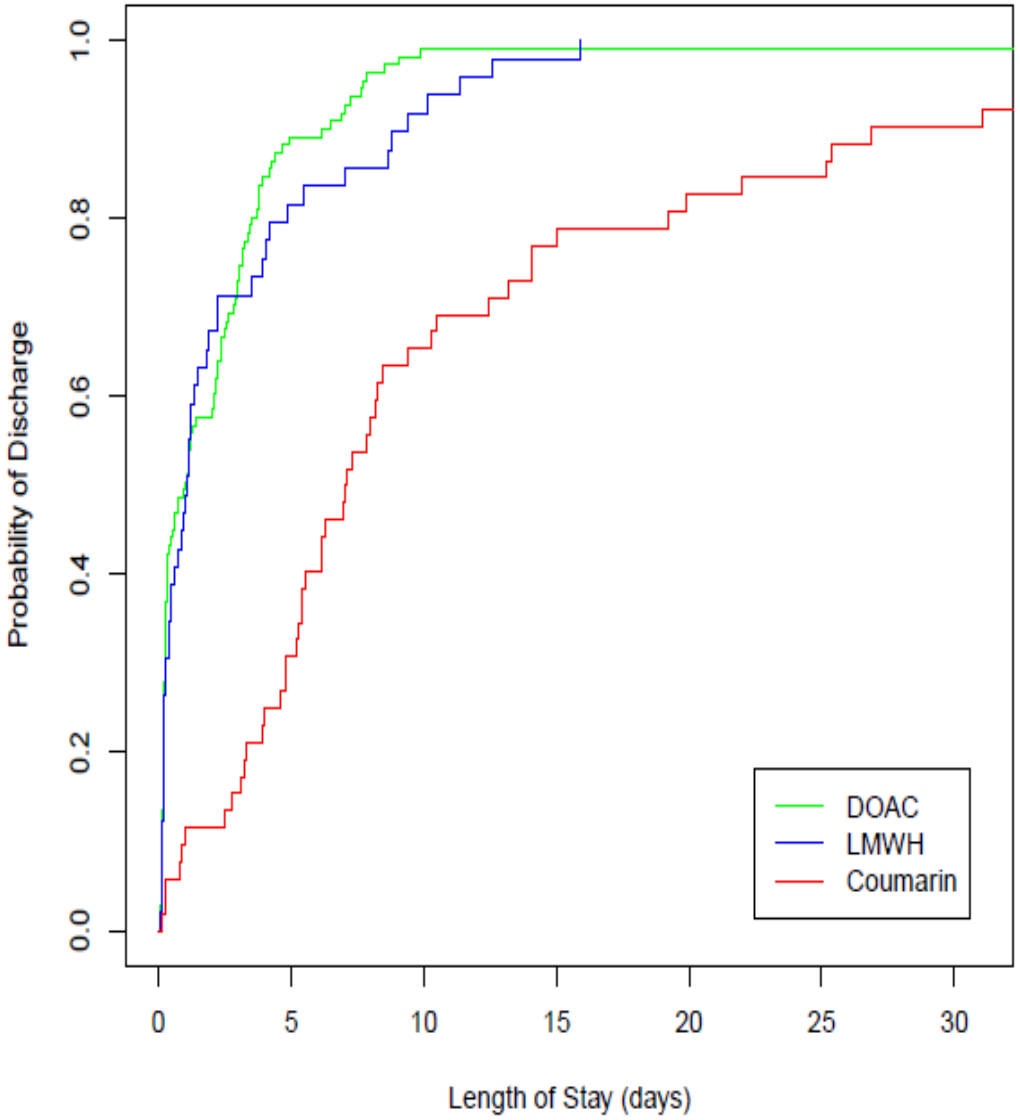
Provoked vs Unprovoked Thrombosis




Hospital Acquired Thrombosis
60
50
40
30
20
10
0
DVT
PE
DVT
PE
2014
2015
Non-HAT
HAT


Length of Stay 2014 vs 2015
400
350
300
250
200
150
100
50
0
Average LOS
Warfarin LOS
LMWH LOS
DOAC LOS
2014
2015

Length of Stay
DOAC vs LMWH vs Warfarin



- DOAC assoc significantly decreased LOS vs Warfarin $p < 0.003$ (3.6×10^{-12})
- LOS of DOAC vs. LMWH not significantly different $p = 0.23$

BHH Guidance

Treatment Decision Making Pathway

Treatment Considerations

Preferred NOAC treatment of choice APIXABAN (easier dose change pathway)

If patient prefers once daily dose regimen - consider Rivaroxaban

Dabigatran would only be used if adverse reactions to Apixaban or Rivaroxaban

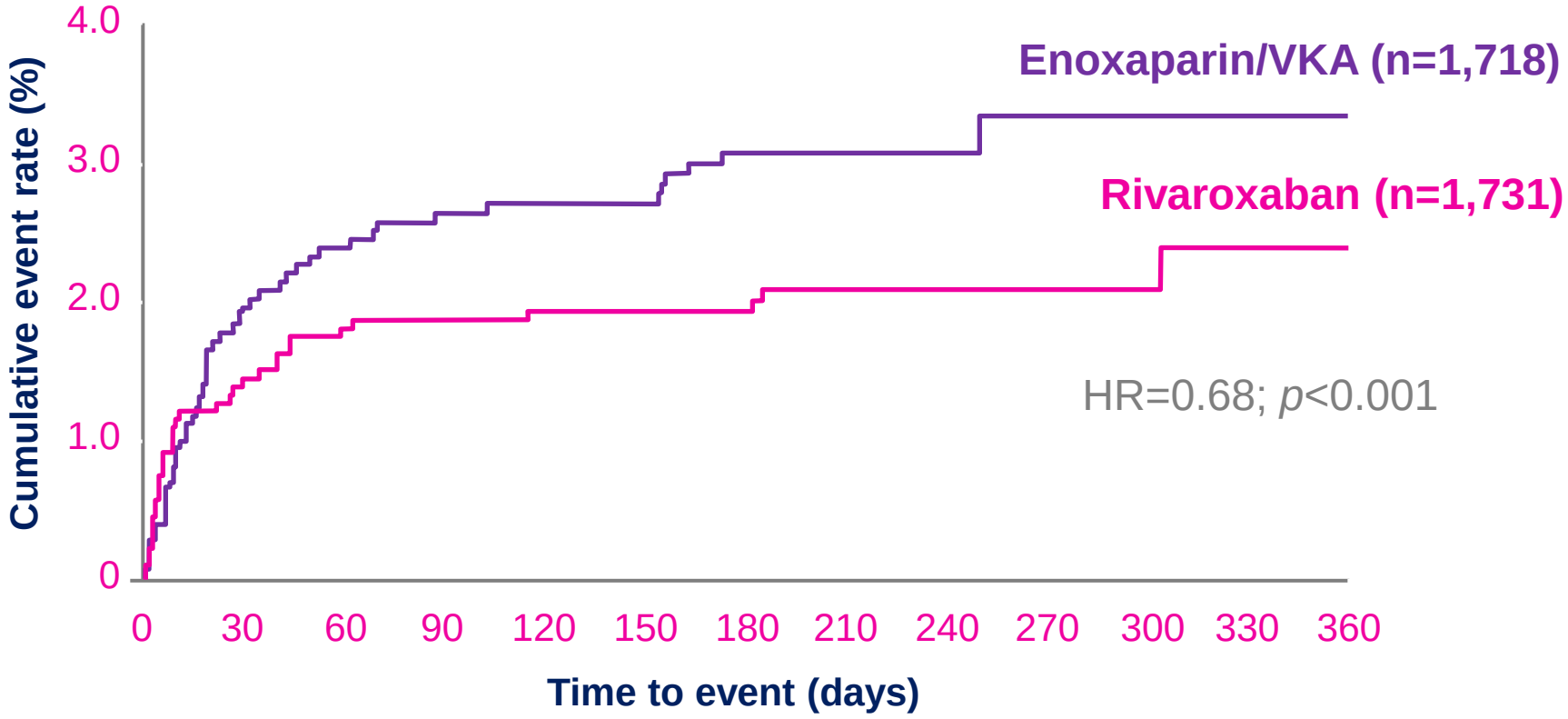
Note dabigatran cannot be placed in compliance aids. (blister packs /dosette boxes)

If patient pregnant or has active cancer - Use LMW heparin alone

Renal impairment:

If patient has calculated GFR <30 mls/min - Use LMW heparin/warfarin

EINSTEIN DVT: primary efficacy outcome - Time to first event



The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

Rivaroxaban in DVT:

principal safety outcome analysis

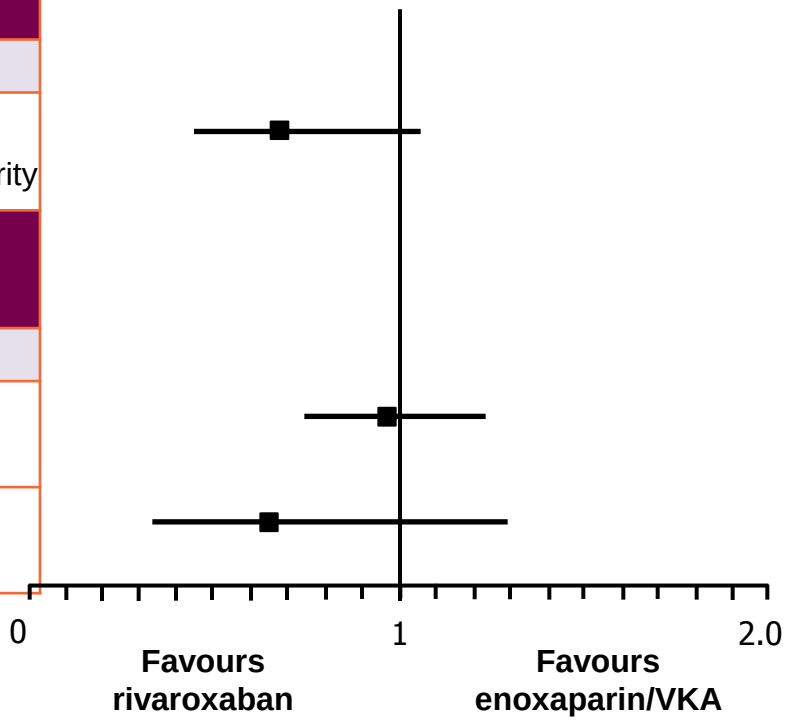
	Rivaroxaban (n=1,718)		Enox/VKA (n=1,711)		HR (95% CI) *p*-value
	n	**(%)**	**n**	**(%)**	
First major or non-major clinically relevant bleeding	**139**	**(8.1)**	**138**	**(8.1)**	**0.97 (0.76–1.22) *p*=0.77**
Major bleeding	14	(0.8)	20	(1.2)	0.65 (0.33–1.30) *p*=0.21
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Non-major clinically relevant bleeding	126	(7.3)	119	(7.0)	

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN-DVT: primary efficacy outcome and key safety outcomes

The EINSTEIN-DVT: open-label, randomised trial comparing rivaroxaban treatment (15 mg twice daily for 21d, then 20 mg once daily for 3, 6 or 12 months) with enoxaparin bridging to VKA therapy in patients with acute symptomatic DVT

	Rivaroxaban (n=1,731)	Enoxaparin/VKA (n=1,718)	HR (95% CI)	*P* Value
Primary efficacy outcome (mean study duration: ~9 months)				
Recurrent VTE, n (%)	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001 Non-inferiority
	Rivaroxaban (n=1,718)	**Enoxaparin/VKA (n=1,711)**	**HR (95% CI)**	***P* Value**
Safety outcomes				
Major or CRNM bleeding, n (%)	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding, n (%)	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21

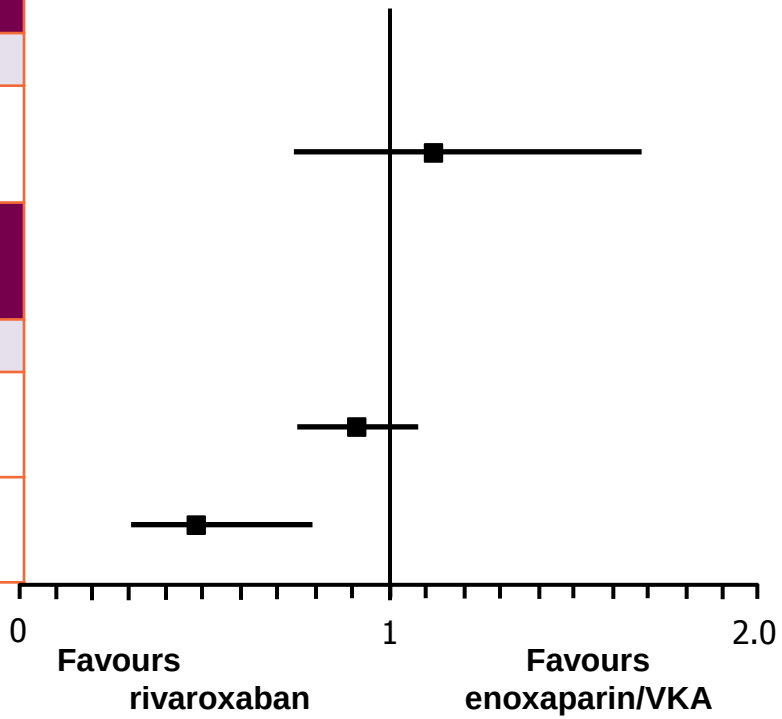


The EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499–2510

EINSTEIN-PE: primary efficacy outcome and key safety outcomes

The EINSTEIN-PE trial open-label, randomised trial comparing rivaroxaban treatment (15 mg BD for 21d, then 20 mg OD for 3, 6 or 12 months) with enoxaparin bridging to VKA therapy in patients with acute symptomatic PE with or without symptomatic DVT

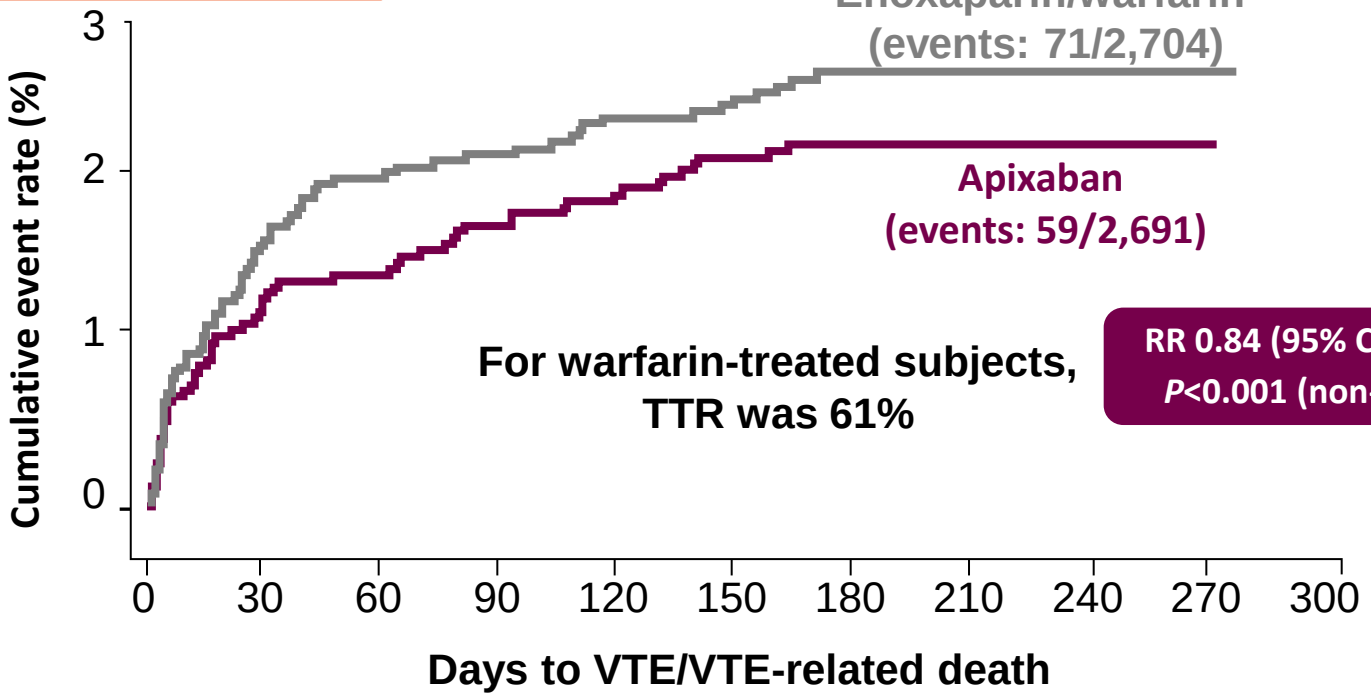
	Rivaroxaban (n=2,419)	Enoxaparin/ VKA (n=2,413)	HR (95% CI)	*P* Value
Primary efficacy outcome (mean study duration: ~9 months)				
Recurrent VTE, n (%)	50 (2.1)	44 (1.8)	1.12 (0.75–1.68)	0.003 Non-inferiority
	Rivaroxaban (n=2,412)	**Enoxaparin/ VKA (n=2,405)**	**HR (95% CI)**	***P* Value**
Safety outcomes				
Major or CRNM bleeding, n (%)	249 (10.3)	274 (11.4)	0.90 (0.76–1.07)	0.23
Major bleeding, n (%)	26 (1.1)	52 (2.2)	0.49 (0.31–0.79)	0.003



The EINSTEIN-PE Investigators. *N Engl J Med*. 2012;366:1287–1297.

AMPLIFY: recurrent VTE or VTE-related death

Primary efficacy outcome

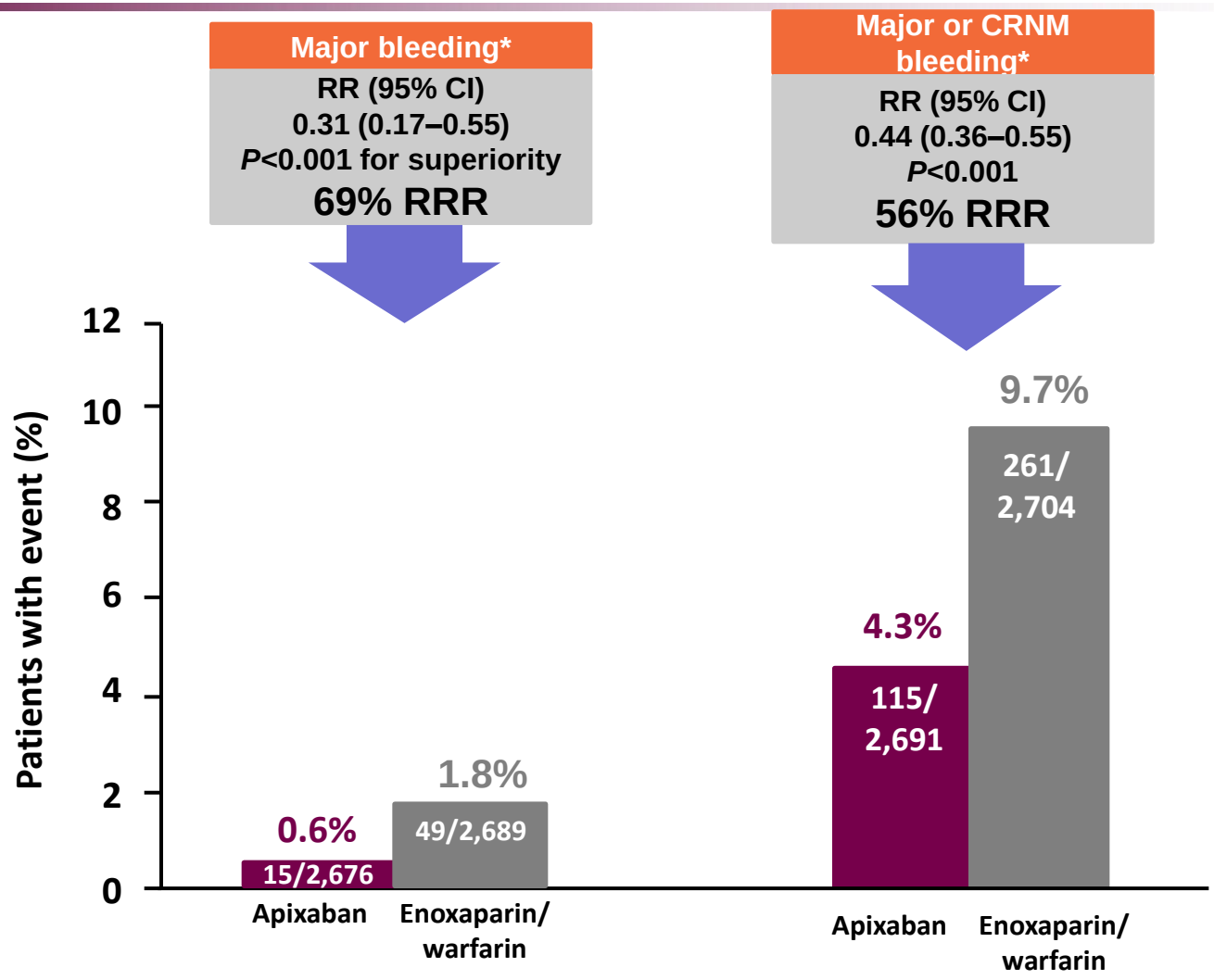


No. of patients at risk

Apixaban	2,691	2,606	2,586	2,563	2,541	2,523	62	4	1	0	0
Eno/war	2,704	2,609	2,585	2,555	2,543	2,533	43	3	1	1	0

Eno, enoxaparin; TTR, time in therapeutic range; War, warfarin.

AMPLIFY: major bleeding vs enoxaparin/warfarin

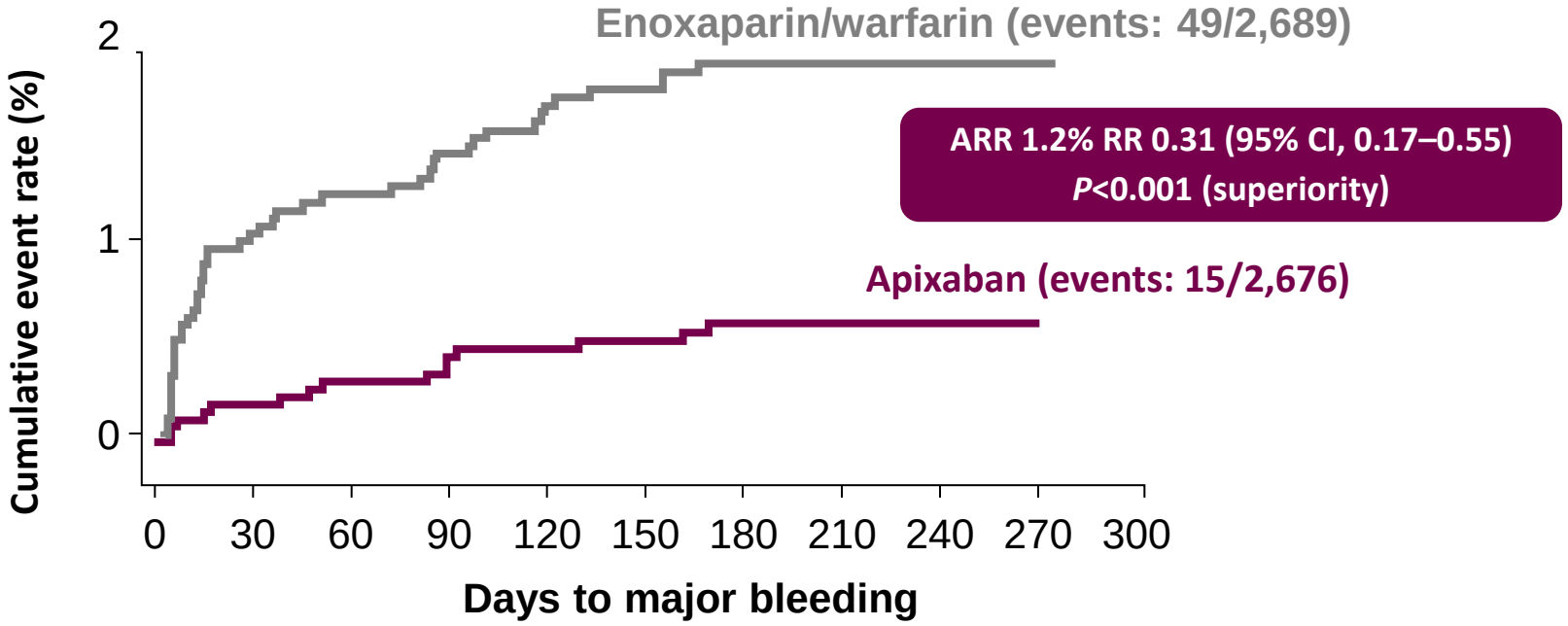


CRNM, clinically relevant non-major; RRR, relative risk reduction.

** For patients who had >1 event, only the first event was counted.*

AMPLIFY: major bleeding

Primary safety outcome



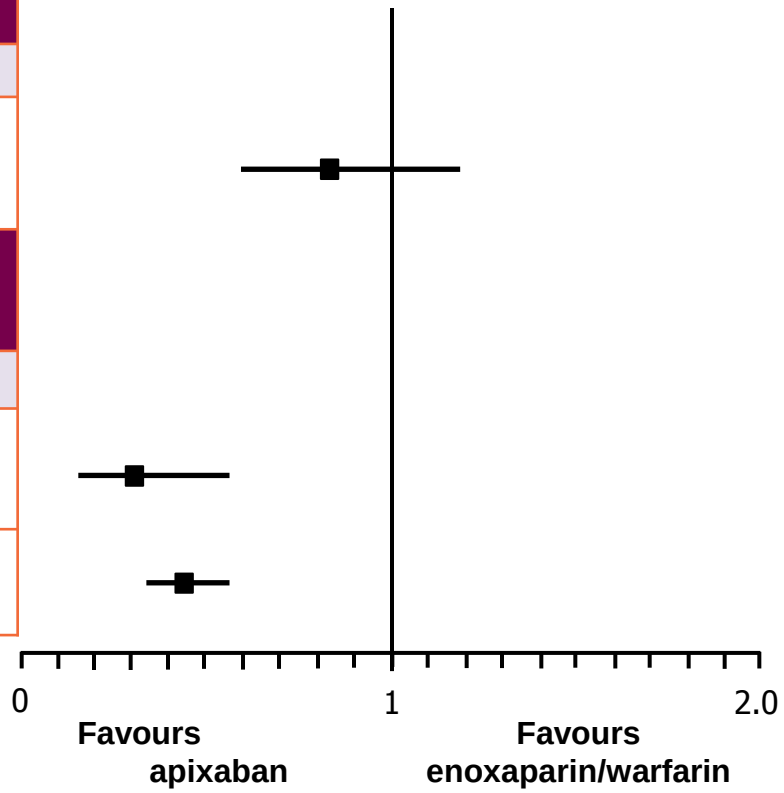
No. of patients at risk

Apixaban	2,676	2,519	2,460	2,409	2,373	2,339	61	4	1	0	0
Eno/war	2,689	2,488	2,426	2,383	2,339	2,310	43	3	1	1	0

AMPLIFY: primary efficacy outcome and key safety outcomes

The AMPLIFY trial was a double-blind, randomised trial comparing 6 months of apixaban treatment with enoxaparin bridging to warfarin therapy in patients with acute symptomatic DVT and/or PE

	Apixaban (n=2,609)	Enoxaparin/ warfarin (n=2,635)	RR (95% CI)	*P* Value
Primary efficacy outcome				
Recurrent VTE or VTE-related death, n (%)	59 (2.3)	71 (2.7)	0.84 (0.60–1.18)	<0.001 Non-inferiority
	Apixaban (n=2,676)	**Enoxaparin/ warfarin (n=2,689)**	**RR (95% CI)**	***P* Value**
Safety outcomes				
Major bleeding, n (%)	15 (0.6)	49 (1.8)	0.31 (0.17–0.55)	<0.001
Major or CRNM bleeding, n (%)	115 (4.3)	261 (9.7)	0.44 (0.36–0.55)	<0.001

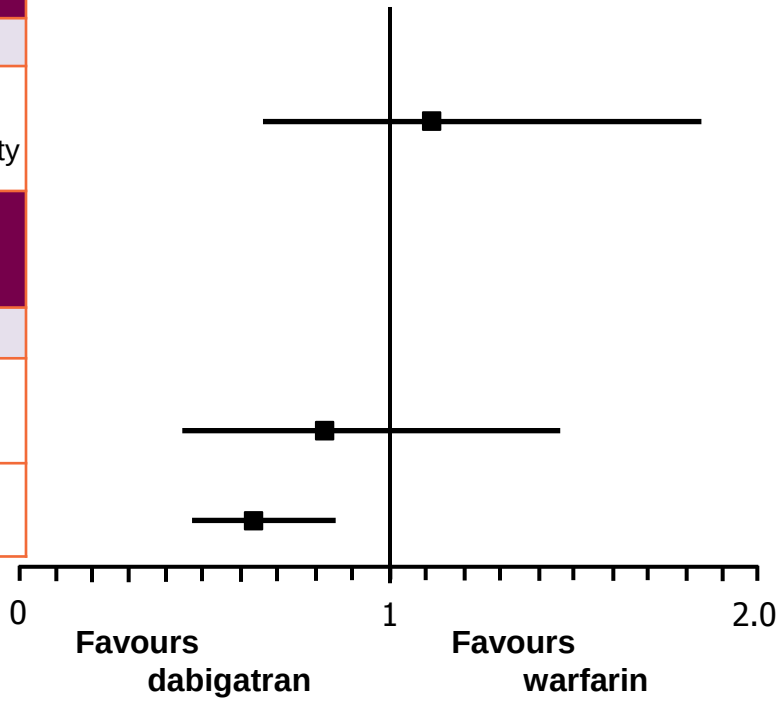


HR, hazard ratio.

RE-COVER: primary efficacy outcome and key safety outcomes

The RE-COVER trial was a double-blind, double-dummy, randomised trial comparing 6 months of dabigatran treatment (150 mg twice daily) with heparin* bridging to dose-adjusted warfarin therapy in patients with acute symptomatic DVT and/or PE

	Dabigatran (n=1,274)	Heparin*/ warfarin (n=1,265)	HR (95% CI)	*P* Value
Primary efficacy outcome				
Recurrent VTE or VTE-related death, n (%)	30 (2.4)	27 (2.1)	1.10 (0.65–1.84)	<0.001 Non-inferiority
	Dabigatran (n=1,273)	**Heparin*/ warfarin (n=1,266)**	**HR (95% CI)**	***P* Value**
Safety outcomes†				
Major bleeding, n (%)	20 (1.6)	24 (1.9)	0.82 (0.45–1.48)	NS
Major or CRNM bleeding, n (%)	71 (5.6)	111 (8.8)	0.63 (0.47–0.84)	0.002



**LMWH, UFH, or fondaparinux.*

†The safety analysis of bleeding events was performed on the basis of the number of patients treated with dabigatran (1,273) or warfarin (1,266), rather than the number assigned to the treatment (1 patient who was assigned to receive dabigatran mistakenly received warfarin instead throughout the study). Events that occurred during the 6-month treatment period plus a 6-day washout period were included.

NS, not specified

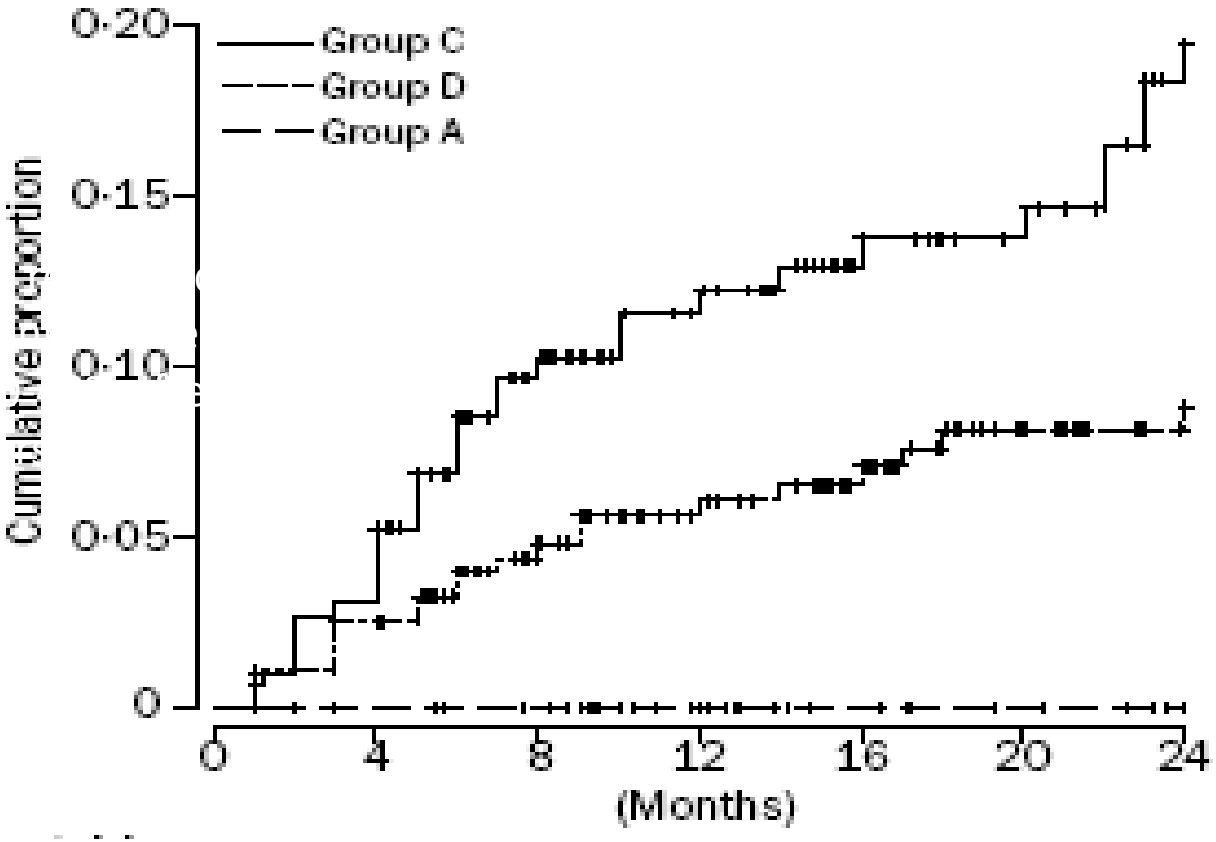
Costings – NICE TA 287

Duration of treatment	Rivaroxaban Cost	Clexane cost	Warfarin Cost	Monitoring costs	VKA/LMWH total
3 months	235	98	5	127	230
6 months	428	98	10	190	298
12 months	811	98	29	318	445

NICE TA287: https://www.nice.org.uk/guidance/ta287/resources June 2013

Recurrence of VTE

Risk of recurrent VTE based on history of index event



Unprovoked

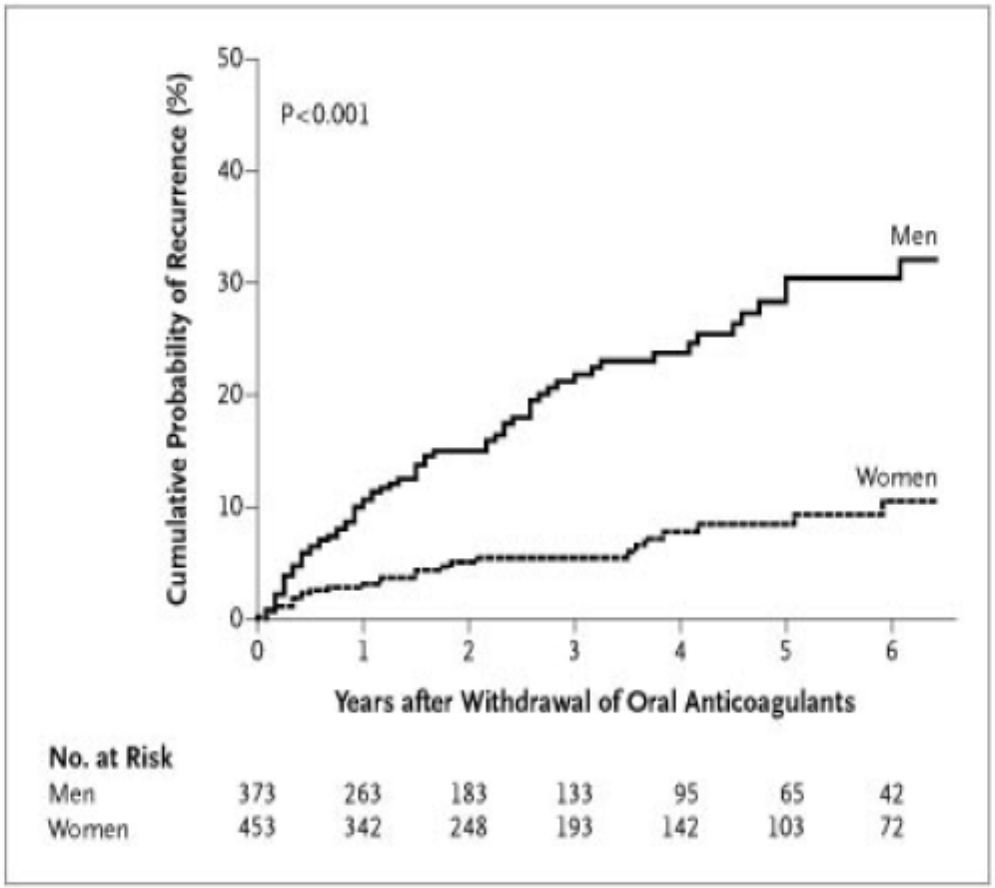
Non-surgical risk factor

Post-surgery

Cambridge cohort

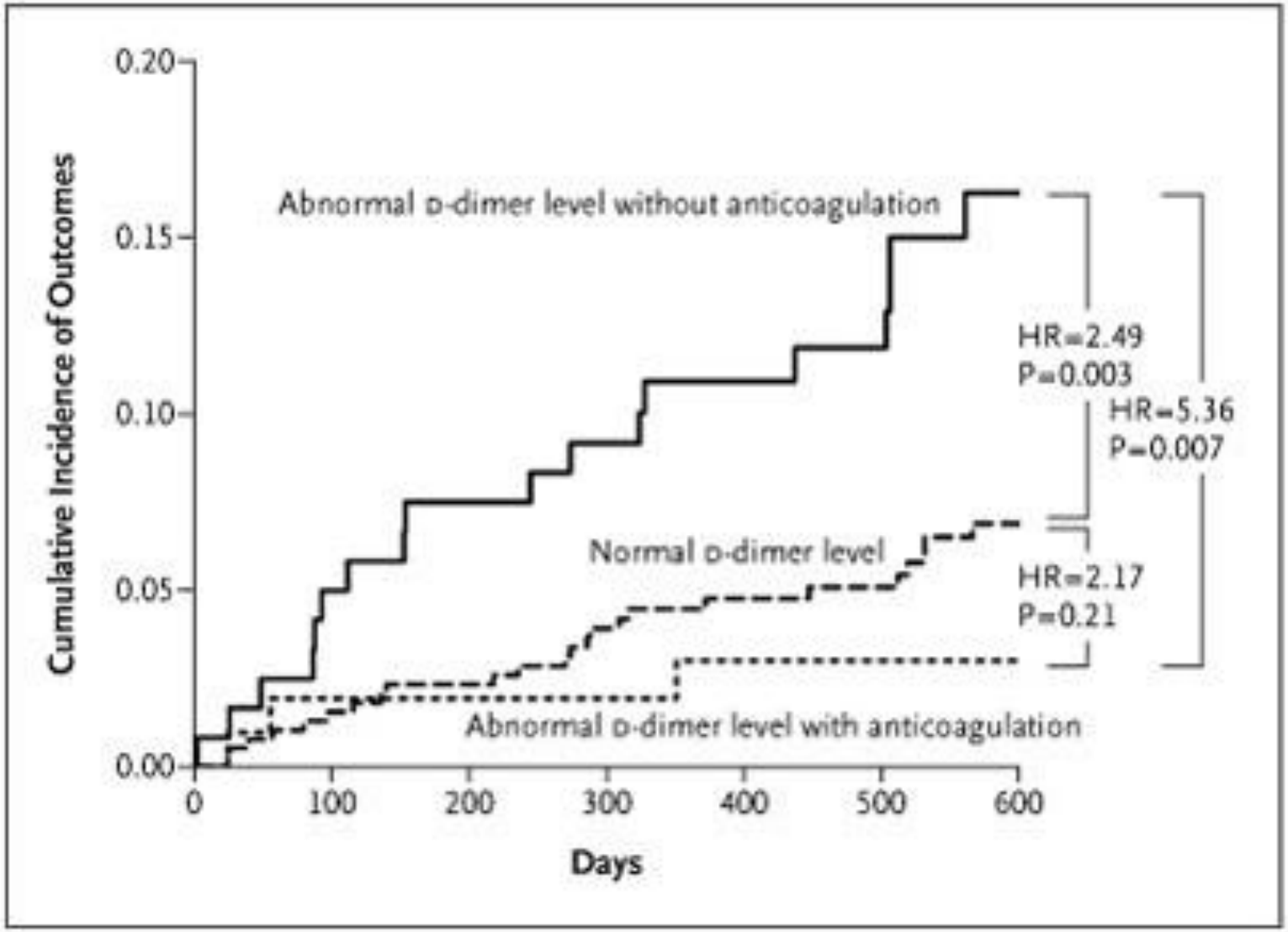
Baglin et al *Lancet* 2003; 362: 523–26

Recurrent VTE according to sex



Kyrle PA, *et al.*, N Engl J Med 2004; 350: 2558-63.

D dimer for prediction of VTE recurrence



Risk score for – Duration of anticoagulation

DASH Prediction Score Derived From Cox Regression Analysis

DASH Predictors (*N = 1,818 VTE cases*)	ß coefficient*	P-value	Recurrence score
1. **D**-dimer abnormal, after stopping AC	0.96	<0.0001	+ 2
2. **A**ge < 50 yr	0.43	0.002	+ 1
3. **S**ex - male	0.58	<0.0001	+ 1
4. **H**ormone use at VTE onset	-1.05	0.002	- 2
DASH Prediction Rule			
DASH Score	≤ 1.0	2.0	≥ 3.0
Annualized VTE Recurrence Rate	3.1%	6.4%	12.3%

*Cox regression coefficients after backward elimination and optimism correction

Table adapted from Tosetto A, Iorio A, Marcucci M, et al. J Thromb Haemost. 2012;366:1019-1025.

NICE CG144

•Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding

•Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT

OTHER SCORES EXIST eg. MENCONTINUE HERDOO2

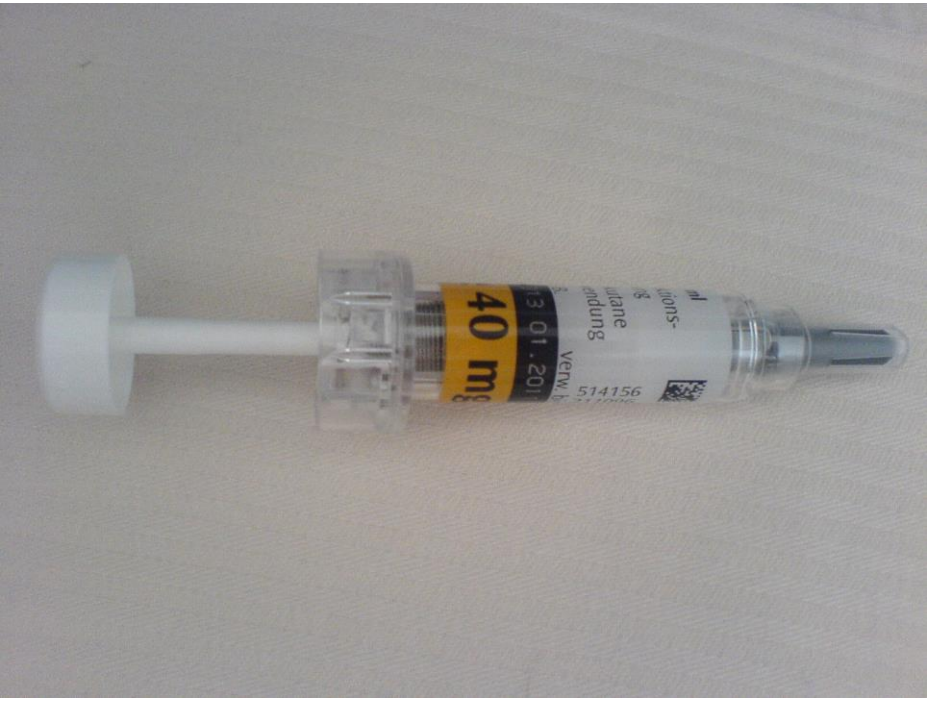
Summary

- BHH / GHH / SHH guidance is for DOAC use in VTE if applicable
- Apixaban first choice
- LMWH is still first line for cancer associated VTE
- Warfarin an option if DOAC inappropriate; AKI, CYP 450 Inducers

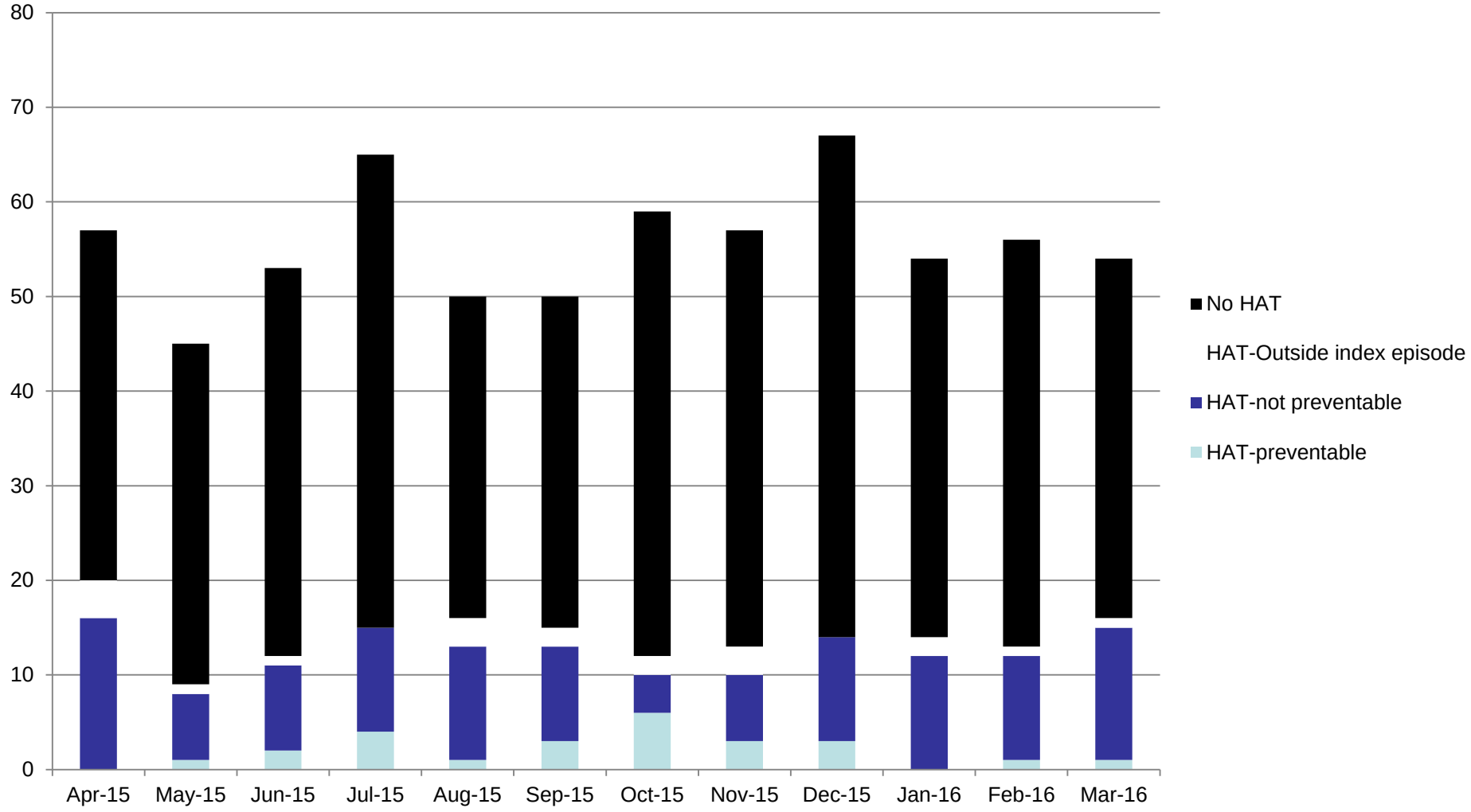
Venous thromboembolism: reducing the risk

Dr Neil Smith
Consultant Haematologist

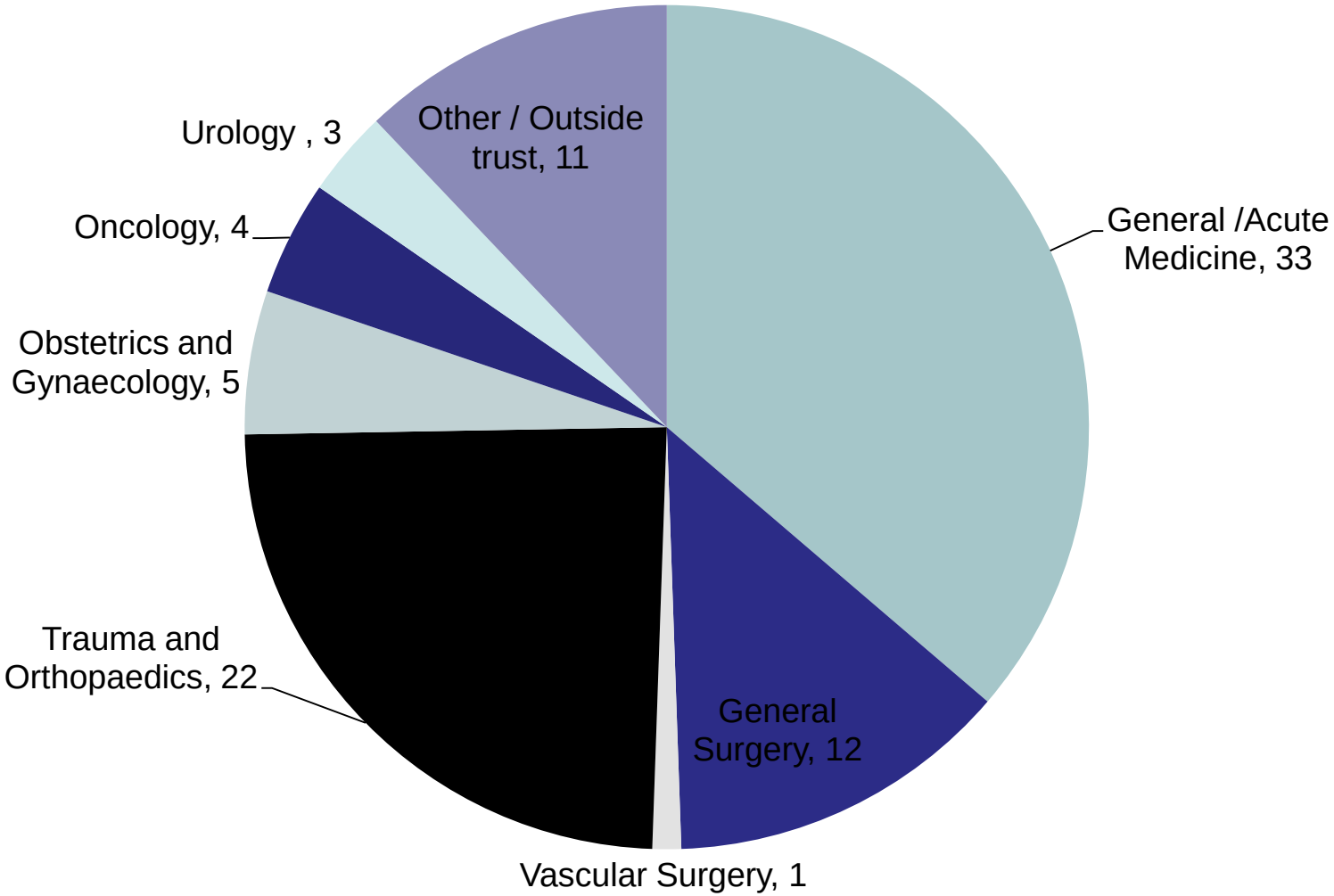
Prescribe thromboprophylaxis



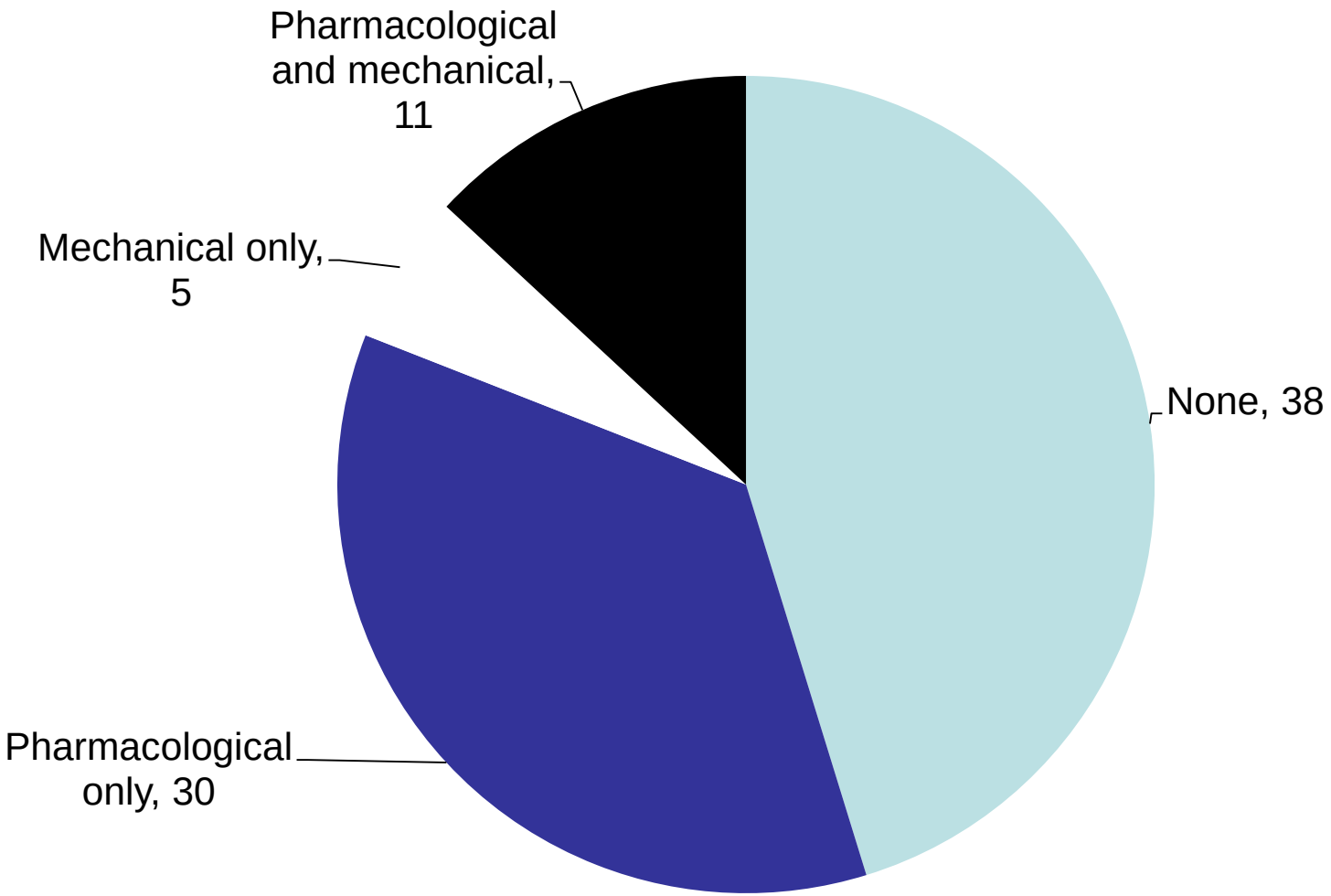
VTEs and HAT – HEFT 2015



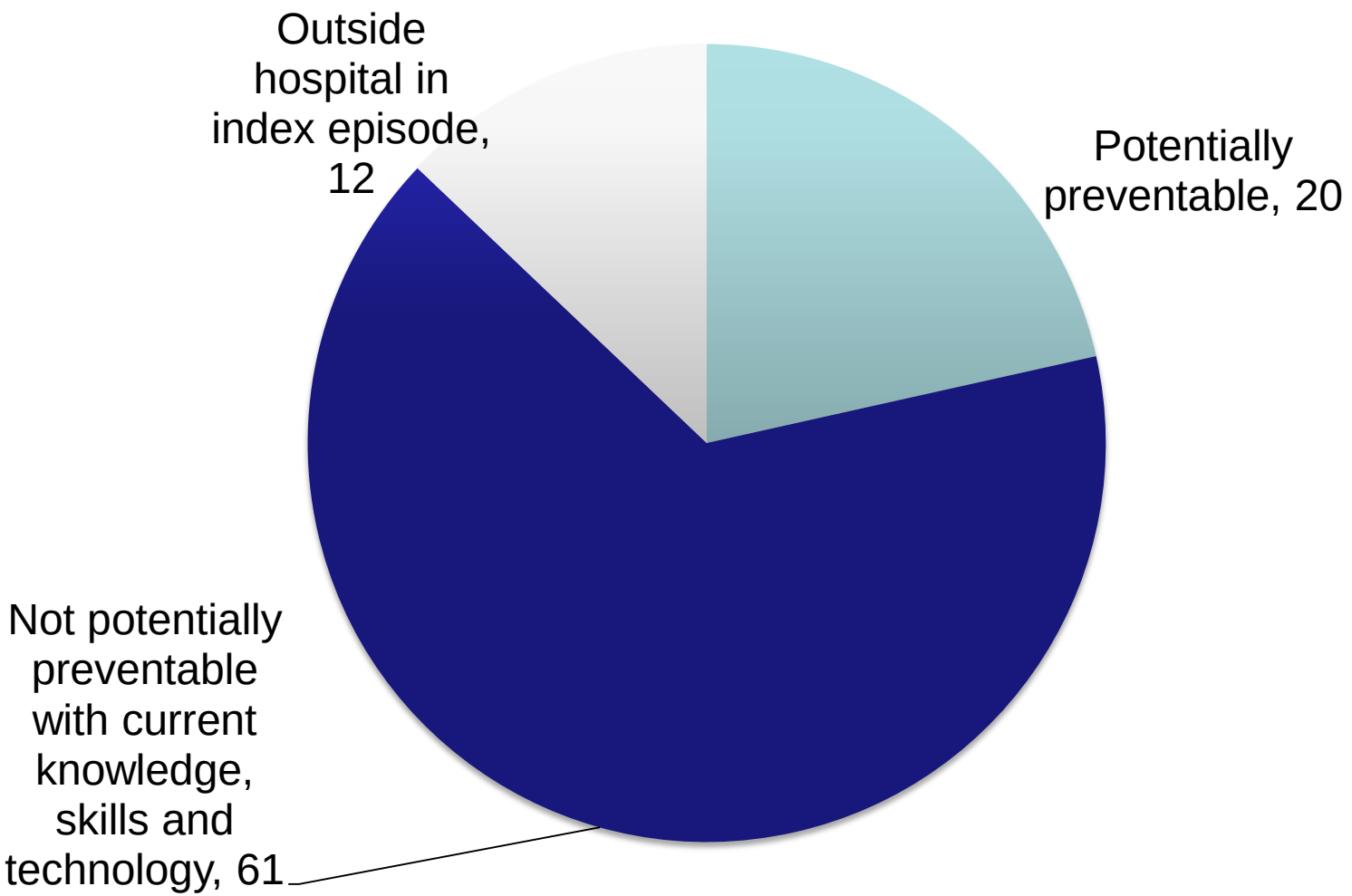
Speciality of index admission



HATs - TP recommended



HAT's ? preventable



Any Questions?