

DOACs and AF Management

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GP Partner Westcliffe Medical Group



Declaration of interests

- The Westcliffe Partnership has received funding from: Abbott, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn4S, INRStar, IRhythm, Medtronic, Oberoi Consulting, Pfizer, Qardio Roche, Sanofi-Aventis, Servier.
- An advisor to: Anticoagulation Europe, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust
- A trustee of Thrombosis UK and AF Association

NICE Quality Standards

- **Statement 1**
 - Adults with non-valvular atrial fibrillation and a CHA₂DS₂-VASc stroke risk score of 2 or above are offered anticoagulation
- **Statement 2**
 - Adults with atrial fibrillation are not prescribed aspirin monotherapy for stroke prevention
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 - Adults with atrial fibrillation taking a vitamin K antagonist who have poor anticoagulation control have their anticoagulation reassessed
- **Statement 5**
 - Adults with atrial fibrillation whose treatment fails to control their symptoms are referred for specialised management within 4 weeks
- **Statement 6 (Developmental)**
 - Adults with atrial fibrillation on long term vitamin K antagonist therapy are supported to self-manage with a coagulometer

NICE Quality Standards

That never was

Case finding and Screening

Diagnosis of Atrial Fibrillation:- NICE CG180

- Perform pulse palpation to assess for the presence of an irregular pulse which may suggest AF in people presenting with:
- breathlessness or dyspnoea,
- Palpitations
- Syncope
- Dizziness
- Chest discomfort
- Stroke or transient ischaemic attack

NB Always perform an ECG to confirm the diagnosis of AF

AF: How can we do better?



of all people with AF in the UK are not receiving full anti-coagulation treatment.

There is an estimated 1.4 million people living with Atrial Fibrillation (AF) in England, however over a third of these people are undiagnosed. It is one of the most important risk factors for stroke, contributing to one in five strokes. If left untreated, AF increases the risk of stroke five-fold.

AF-related strokes are often more severe with higher mortality and greater disability. Treatment with an anticoagulant significantly reduces the risk of stroke in people with AF.

The Stroke Association, in partnership with [Public Health England](#), [Royal College of Physicians](#), [Royal College of General Practitioners](#) and [British Heart Foundation](#) have created 'AF: How can we do better?'

'AF: How can we do better?' is a free user-friendly document showing the state of atrial fibrillation care in [England](#) and each of its CCGs.

Using data from the Quality and Outcomes Framework (QOF), Public Health England (PHE), Sentinel Stroke National Audit Programme (SSNAP) and NHSIQ we have compiled a comprehensive summary of the atrial fibrillation care.

You can use these reports to speak to your local CCG or GP about what they're doing to treat atrial fibrillation and prevent stroke in your area.

High blood pressure and stroke

[View all publications](#)

Useful links

- [What is atrial fibrillation](#)
- [Resources for professionals](#)

Share

<https://www.stroke.org.uk/3UF>



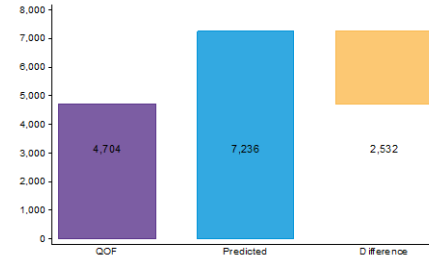
AF: How can we do better?

NHS BRADFORD DISTRICTS CCG

Detection of AF in CCG

Source: GOF 2015/16, BCVM 2015

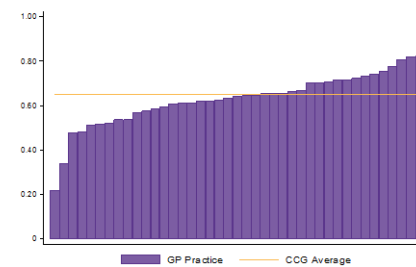
1.4 million people in England are estimated to have atrial fibrillation (AF) (2.4% of the adult population).



Undiagnosed AF in CCG

Source: GOF 2015/16, BCVM 2015

There is significant variation in the proportion of their patients with AF who remain undiagnosed.



AF Strokes in CCG

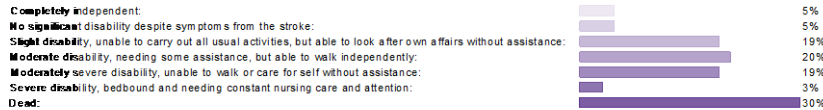
Source: ISMAP 2016

AF is a major risk factor for stroke and a contributing factor to one in five strokes. Treatment with an oral anticoagulant medication (e.g. warfarin) reduces the risk of stroke in someone with AF by two thirds.



AF Strokes: Outcome after discharge in people NOT anticoagulated before their stroke in CCG

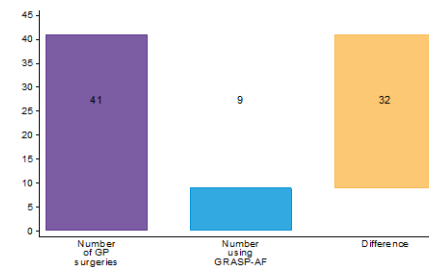
Source: ISMAP 2016



Case finding of AF in CCG

Source: ISMAP 2016

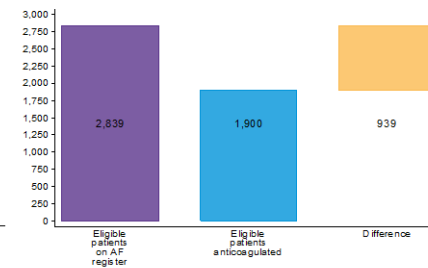
GRASP-AF is a free software tool that GP practices can use to help identify and improve the management of patients with AF.



Number of AF patients anticoagulated in CCG

Source: GOF 2015/16

Nationally 31% of eligible patients do not receive anticoagulation. This includes excepted patients, but some practices except far fewer than others.



Stroke Association partnership with:



Screening for atrial fibrillation

Recommendations	Class	Level
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy.	I	B
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.	IIa	B
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B

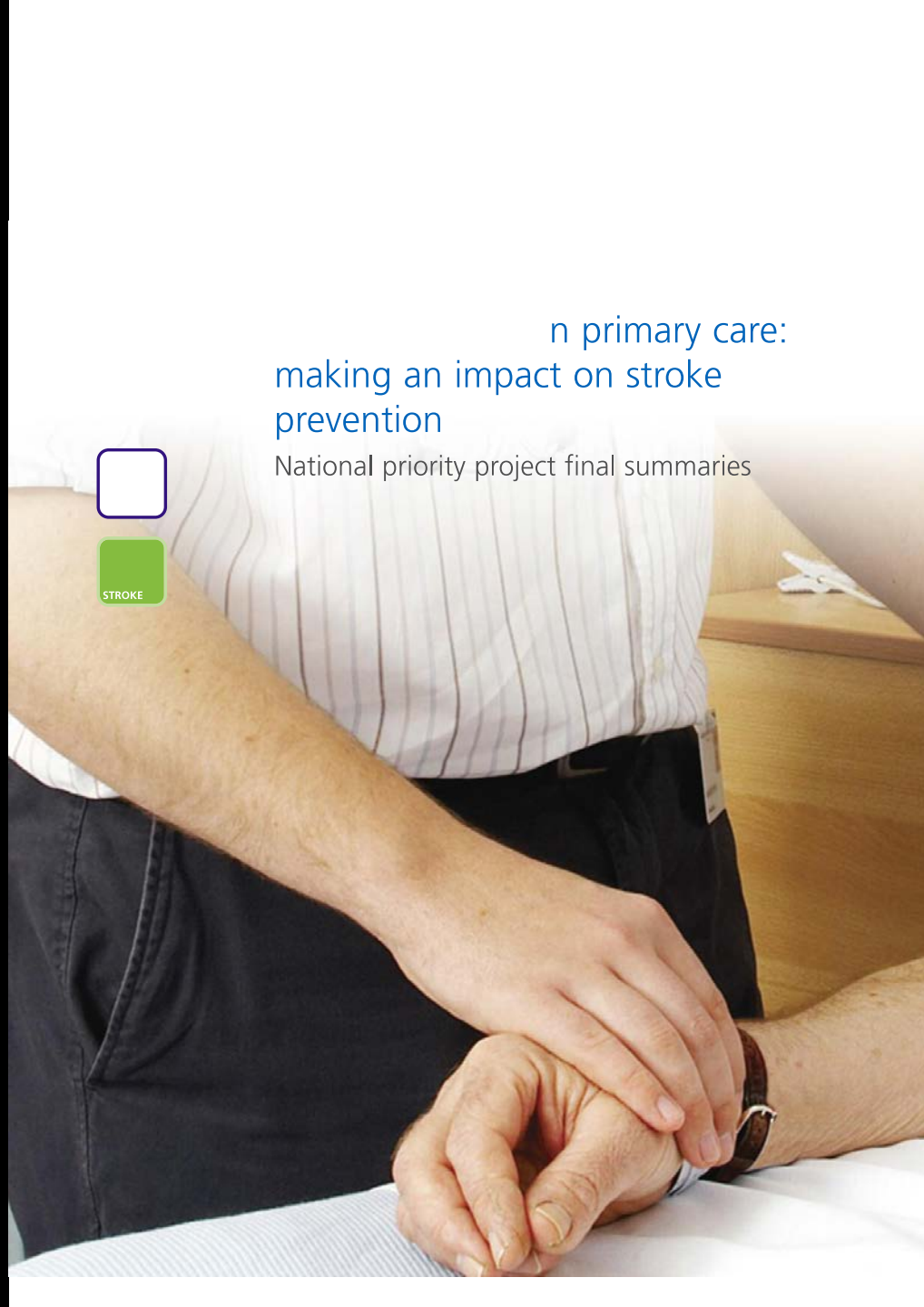
Screening for Atrial Fibrillation in People aged 65 and over

A report
for the National Screening Committee

May 2014

n primary care:
making an impact on stroke
prevention

National priority project final summaries



Atrial Fibrillation Screening Project

Bedfordshire and Hertfordshire Heart and Stroke Network, Bedfordshire Primary Care Trust, 23 GP Practices

Duration of project

October 2008

Scope of project

Opportunistic pulse screening at flu clinics

What we did

- One practice originally targeted for pulse screening patients during flu clinics – Oct 2007. (see publication 'Heart Improvement: Atrial Fibrillation in Primary Care - National Priority Project' (www.heart.nhs.uk/priority_projects/summary_documents/af_summary.pdf)
- Subsequently a local enhanced service (LES) was developed to encourage wider uptake
- One primary care trust (PCT) implemented this during the flu season of 2008
- Currently working with the three other PCTs in the network through local implementation groups and practice based commissioning groups (PBC) to role out the LES for the 2009 flu season.

Key challenges

Engaging PBC groups.

What went well

AF registers significantly improved in practices that took up the LES.

Key learning from work

- Communication is essential
- Posters and leaflets developed for patients
- Ensure district general hospital (DGH) services are aware of this initiative, as this can increase referrals into the cardiology department significantly
- Important to have AF management pathways in place to support initiative.

Outcomes

- 23 practices used the LES
- 6,000 patients screened
- 122 new patients added to the AF register.

Costs incurred

Payment to practices - 10p per patient screened, £60 per patient added to AF register.

Patient, carer and staff involvement

Patients, clinicians and practice staff all felt the project was worthwhile and caused very little disruption to the flu clinic.

The patients in particular were very pleased with the extra service when they understood the importance of the screening.

Resources and tools developed to support the changes

Available for sharing by contacting project lead

- Local enhanced service.

Future plans

- Continued expansion of the pulse screening in GP practices across Bedfordshire and Hertfordshire and improve AF awareness in relation to stroke prevention
- Offer regular training on the management of AF.

Sites outside your network where your approach has been adopted by others

North Yorkshire
Essex.

Contact details

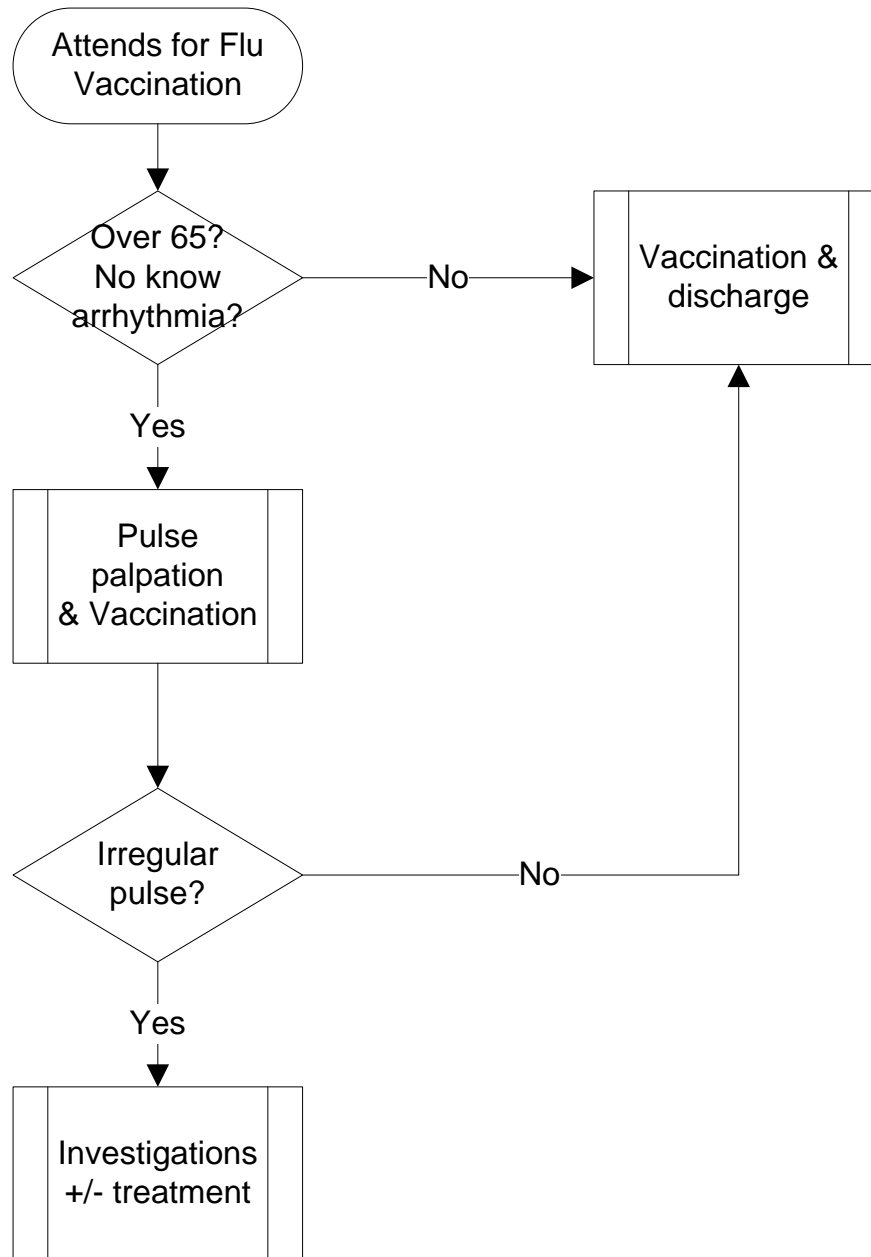
Project and clinical lead:
Delyth Williams
Email: Delyth.Williams@bedfordshire.nhs.uk

Undiagnosed AF



QoF Prevalences

- AF
 - National 1.2%
 - North East Essex 1.6% average (up to 4.8% in some practices)
- Stroke
 - National 1.6%
 - North East Essex 1.7% (up to 4% in some practices)



Outcomes



37/43 practices in N E Essex Signed up to LES

- **34,201 patients screened** in 6 weeks
 - 3154 Patients found with irregular pulse (9.2%)
 - 189 Patients found with AF (0.55%)
 - 342 Patients found with other Arrhythmias (0.99%) **including 2 in Complete H. Block!**

Outcomes



37/43 practices in N E Essex Signed up to LES

- **34,201 patients screened** in 6 weeks

- 3154 Patients found with irregular pulse (9.2%)

- 189 Patients found with AF (0.55%)

- 242 Patients found with other Arrhythmias

17 ECGs for every AF diagnosed

Take the Opportunity



British Heart
Foundation

Action in the Community

Know Your Pulse Campaign

46,000 new cases of atrial fibrillation are diagnosed each year which cause around 12,500 strokes each year. Improving diagnosis and anticoagulation therapy would prevent 4,500 strokes each year and 3,000 deaths.

Together we are calling on the Government to introduce pulse checks to screen for atrial fibrillation in:

- + NHS Health Check
- + Flu vaccination clinics

This could help prevent **4,500 strokes** and **3,000 deaths** per year.

Support Our Campaign

Take two minutes to help us introduce pulse checks in the NHS and bring our heart to life. Email your MP to ask them to support the Know Your Pulse campaign.

To get started, simply enter your postcode;

Enter your postcode

PARTICIPATE

1616

People have supported the



Bayer HealthCare
Bayer Schering Pharm

Pulse Check App

Download the FREE iPhone App

Go »

- Take the pulse
- Record ECG

AF Detection on iPhone ECG



	Sensitivity	Specificity	Accuracy	Kappa
Learning set (n = 109)				
Cardiologist A	100%	90%	94%	0.87
Cardiologist B	95%	94%	95%	0.88
Original algorithm	87%	97%	94%	0.86
Optimized algorithm	100%	96%	97%	0.94
Validation set (n = 204) Algorithm was optimized by increasing weighting of absence of P waves				
Optimized algorithm	98%	97%	97%	0.92

MyDiagnostick

- Acquires a one minute ECG (Lead I)
- Performs ECG analysis and provides diagnostic outcome directly after ECG acquisition
- Diagnostic outcome is simply red (AF) or green (No AF) easy interpreted by physician and patient
- Web-portal for ECG viewing, storage and management

- 573 patients ≥ 65 years old attending flu clinic and 95 patients had an irregular pulse
- 21 had prior AF, 68 were invited for ECG and 39 attended
- 2 new cases of AF were diagnosed

Rhys GC, et al. Keele University, UK

- 61 pts (age 70.1 ± 5.2 years) of 676 pts (age 74 ± 7.1 years) attending for flu vaccine had AF
- Correct diagnosis in 55 pts (prevalence 8.1%)
- 44 pts (6.5%) were known with AF, but 11 pts (1.6%) were not
- Mean CHA₂DS₂-VASc-score of 3

Tieleman R et al, Europace 2014 – in press



Zenikor



Stepwise screening for atrial fibrillation in a 75-year old population – implications for stroke prevention

Johan Engdahl, Lisbeth Andersson, Maria Mirskaya, Mårten Rosenqvist*

Department of Medicine, Hallands Hospital Halmstad, Sweden

* Karolinska Institute, Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden

Conclusion

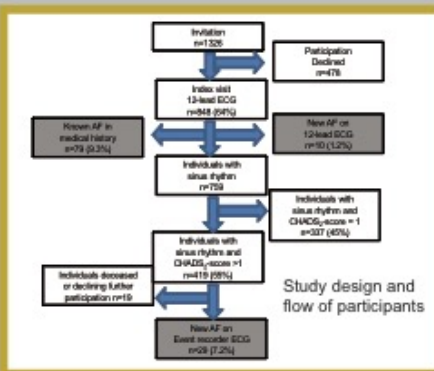
Stepwise risk factor-stratified AF screening in a 75-year old population yields a large share of candidates for OAC treatment for stroke prevention.



The handheld ECG unit from Zenicor Medical Systems.

Background

Atrial fibrillation (AF) is a frequent source of cardiac emboli in patients with ischemic stroke. AF may be asymptomatic and therefore undiagnosed. As oral anticoagulation (OAC) treatment is highly effective for stroke prevention, screening for silent AF seems suitable in risk populations. Little is however known on the yield and cost-effectiveness of such screening. The aim of this study was to explore by extended screening the prevalence of asymptomatic AF in a population aged 75-76 years.

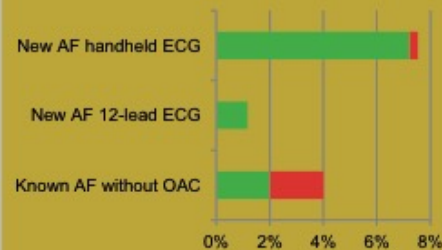


Results

1326 inhabitants were invited of whom 848 (64%) participated. Previously undiagnosed silent AF was found in 10 (1%) among 848 who recorded 12-lead ECG. Among 79 persons with known AF, 32 (41%) were not on OAC treatment. Among 400 persons with at least 2 risk factors for stroke who completed the hand-held ECG recording, 29 (7.2%, 95% CI 5.1-10.2) were diagnosed with paroxysmal AF. Thus 71/848 (8.4%, 95% CI 6.7-10.4) of the screened population were candidates for new OAC treatment.

Methods

All inhabitants in the municipality of Halmstad, Sweden aged 75-76 years were invited to a stepwise screening program for AF. As a first step, participants recorded a 12-lead ECG and reported their relevant medical history. Those with sinus rhythm on 12-lead ECG, no history of AF and at least 2 risk factors according to CHADS2 were invited to a 2 week recording period using a hand-held ECG asked to record 20 or 30 seconds twice daily and if palpitations occurred.



Yield of different methods of identifying patients with AF and an indication for OAC treatment and the proportion actually starting OAC treatment. Green bars indicate the proportion starting OAC treatment, red bars denotes the proportion of patients who did not.

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF)

EMBRACE Study



The NEW ENGLAND
JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Atrial Fibrillation in Patients with Cryptogenic Stroke

David J. Gladstone, M.D., Ph.D., Melanie Spring, M.D., Paul Dorian, M.D., Val Panzov, M.D., Kevin E. Thorpe, M.Math., Judith Hall, M.Sc., Haris Vaid, B.Sc., Martin O'Donnell, M.B., Ph.D., Andreas Laupacis, M.D., Robert Côté, M.D., Mukul Sharma, M.D., John A. Blakely, M.D., Ashfaq Shuaib, M.D., Vladimir Hachinski, M.D., D.Sc., Shelagh B. Coutts, M.B., Ch.B., M.D., Demetrios J. Sahlas, M.D., Phil Teal, M.D., Samuel Yip, M.D., J. David Spence, M.D., Brian Buck, M.D., Steve Verreault, M.D., Leanne K. Casaubon, M.D., Andrew Penn, M.D., Daniel Selchen, M.D., Albert Jin, M.D., David Howse, M.D., Manu Mehdiratta, M.D., Karl Boyle, M.B., B.Ch., Richard Aviv, M.B., Ch.B., Moira K. Kapral, M.D., and Muhammad Mamdani, Pharm.D., M.P.H., for the EMBRACE Investigators and Coordinators*

N Engl J Med 2014; 370:2467-2477 | [June 26, 2014](#) | DOI: 10.1056/NEJMoa1311376

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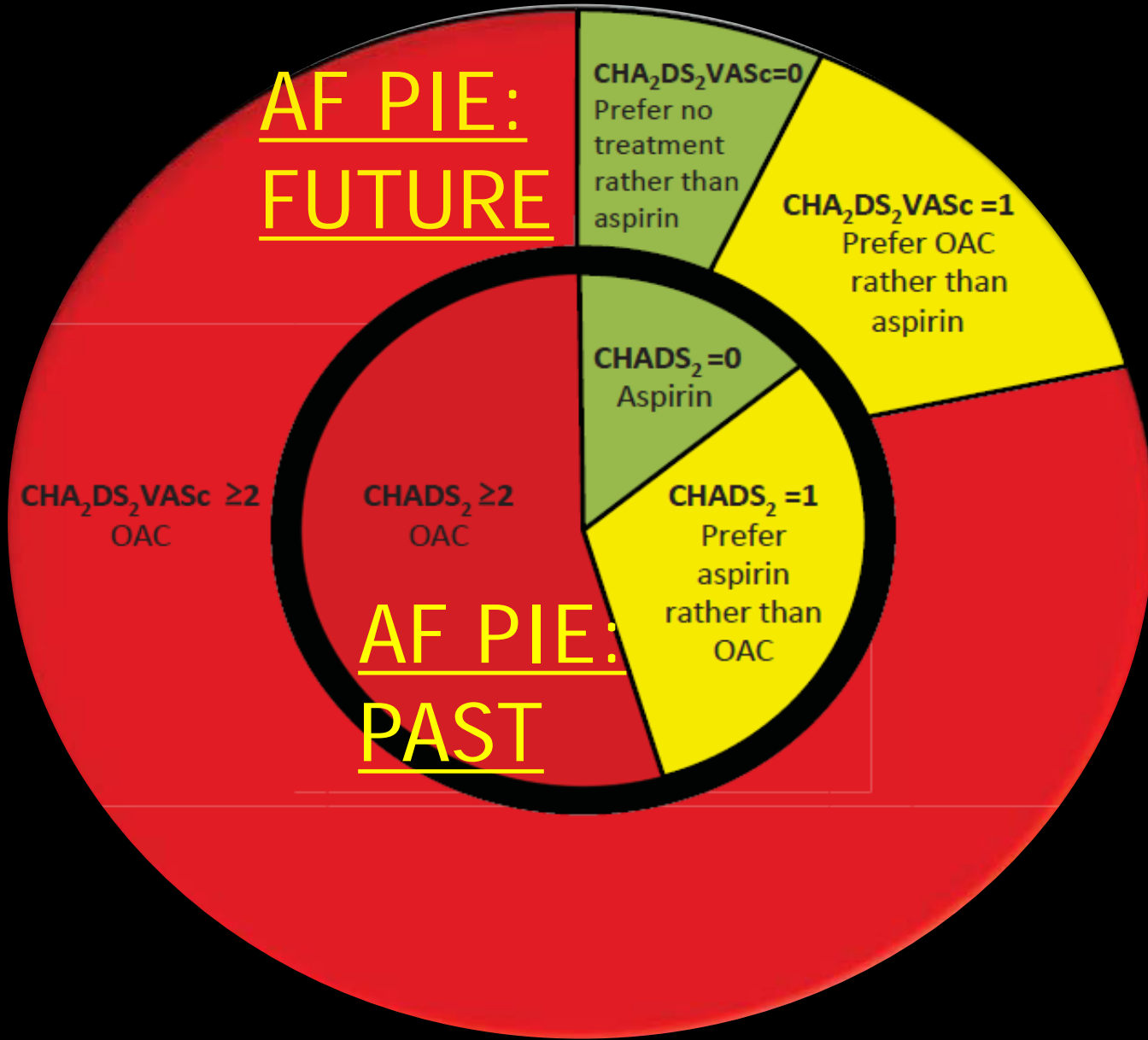
- **Statement 6 (Developmental)**

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Stroke risk in AF: CHA₂DS₂VASc

CHA ₂ DS ₂ VASc	Score
Cardiac failure	1
Hypertension	1
Age >75 yrs	2
Diabetes mellitus	1
Stroke or TIA (previous history)	2
Vascular disease (IHD, PAD)	1
Age 65-74 yrs	1
Sex Category	1

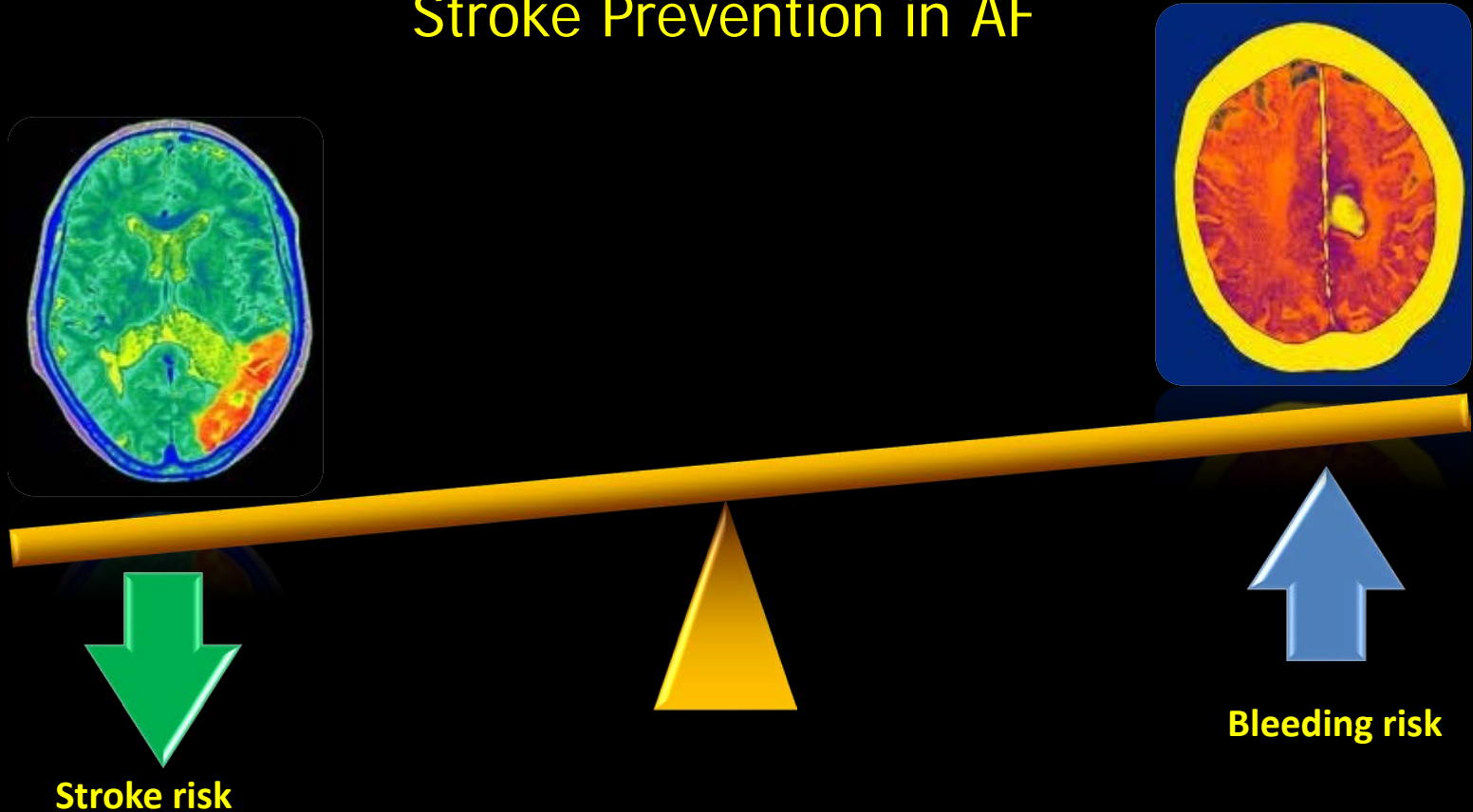
AF PIE:
FUTURE



AF PIE:
PAST

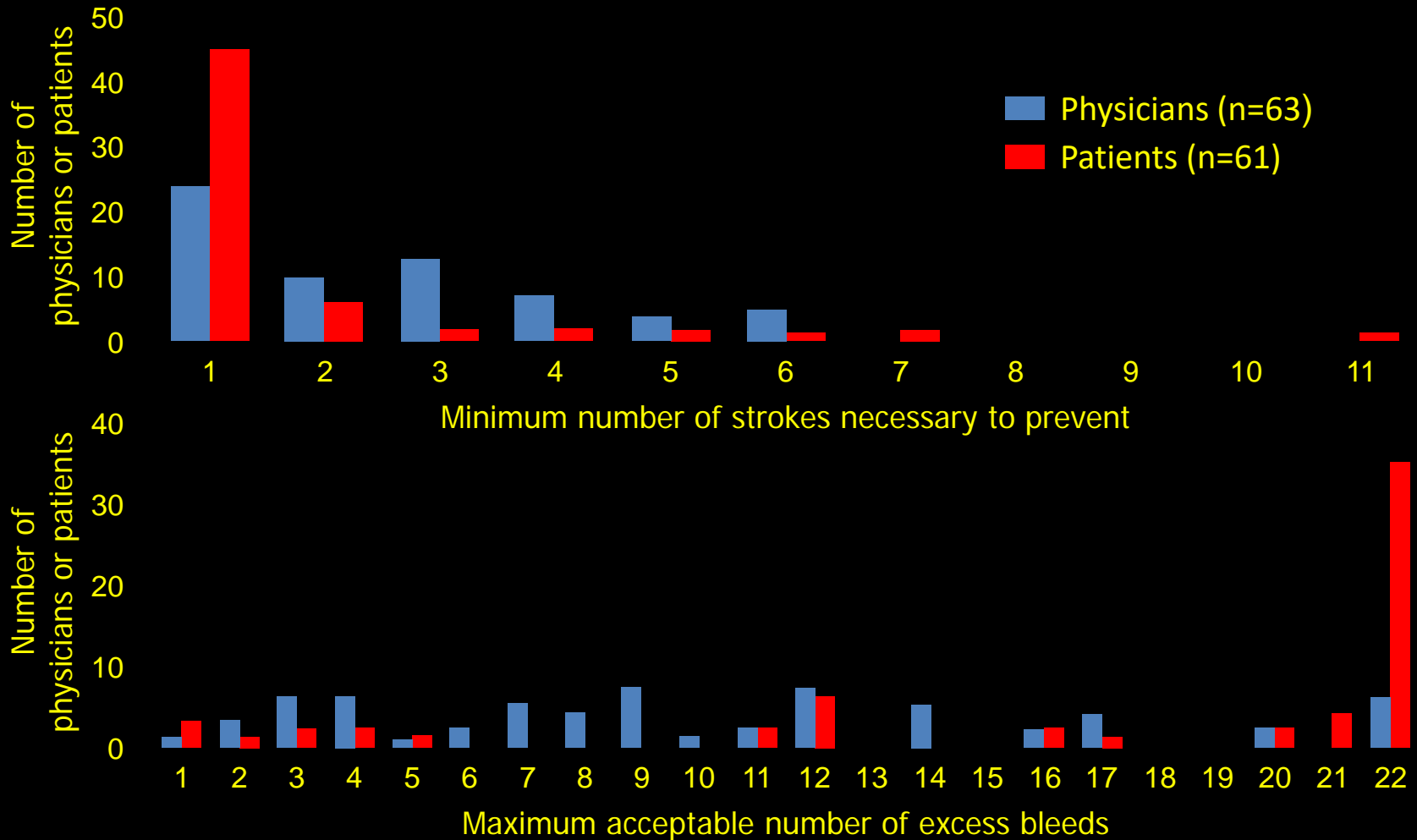
Bleeding Risk

Stroke Prevention in AF



Balancing the benefits and risks

Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study



Risk factors for stroke and thrombo-embolism in non-valvular AF

Clinically relevant non-major risk factors

Major risk factors

Previous stroke

TIA or systemic embolism

Age ≥ 75 years

Clinically relevant non-major risk factors

CHF or moderate to severe LV systolic dysfunction [e.g. LV EF $\leq 40\%$]

Hypertension

Diabetes mellitus

Age 65–74 years

Female sex

Vascular disease

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Clinical characteristics comprising the HAS-BLED bleeding risk score

HAS-BLED risk criteria	Points awarded
H ypertension (i.e. Uncontrolled BP)	1
A bnormal renal and liver function (1 point each)	1 or 2
S troke	1
B leeding	1
L abile INRs	1
E lderly (e.g. age >65 years, frail condition)	1
D rugs or alcohol (1 point each)	1 or 2
	Maximum 9 points

Modifiable risk factors for bleeding in anticoagulated patients with atrial fibrillation

Modifiable bleeding risk factors:

Hypertension (especially when systolic blood pressure is >160 mmHg)

Labile INR or time in therapeutic range $<60\%$ in patients on vitamin K antagonists

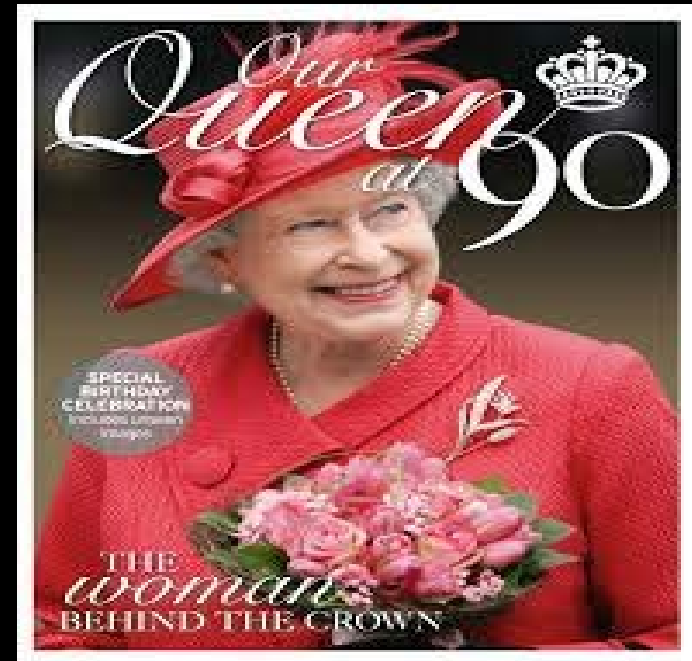
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs

Excess alcohol (≥ 8 drinks/week)

Frailty as a risk

Frailty as a risk

- 90y woman
- Lives in supervised accommodation
- Assistance with personal care (PADL)
- Assistance with shopping, messages (IADL)



Frailty as a risk

Prospective study of a cohort of 220 acute inpatients aged ≥ 70 years with AF
 Patients followed up at 6 months = 207
 Frail = 130; Not Frail = 77

	Warfarin (n=83)			Antiplatelet (n=98)			None (n=26)		
	Haem	Stroke	Both	Haem	Stroke	Both	Haem	Stroke	Both
Frail	30%	7%	37%	25%	9%	34%	8%	29%	38%
Not Frail	19%	2%	21%	14%	5%	18%	0%	50%	50%
Total	23%	4%	27%	22%	8%	31%	8%	31%	38%

Falls as a risk

- Cost benefit analysis shows the number of falls on average likely to cause greater risk than benefits with warfarin = 295

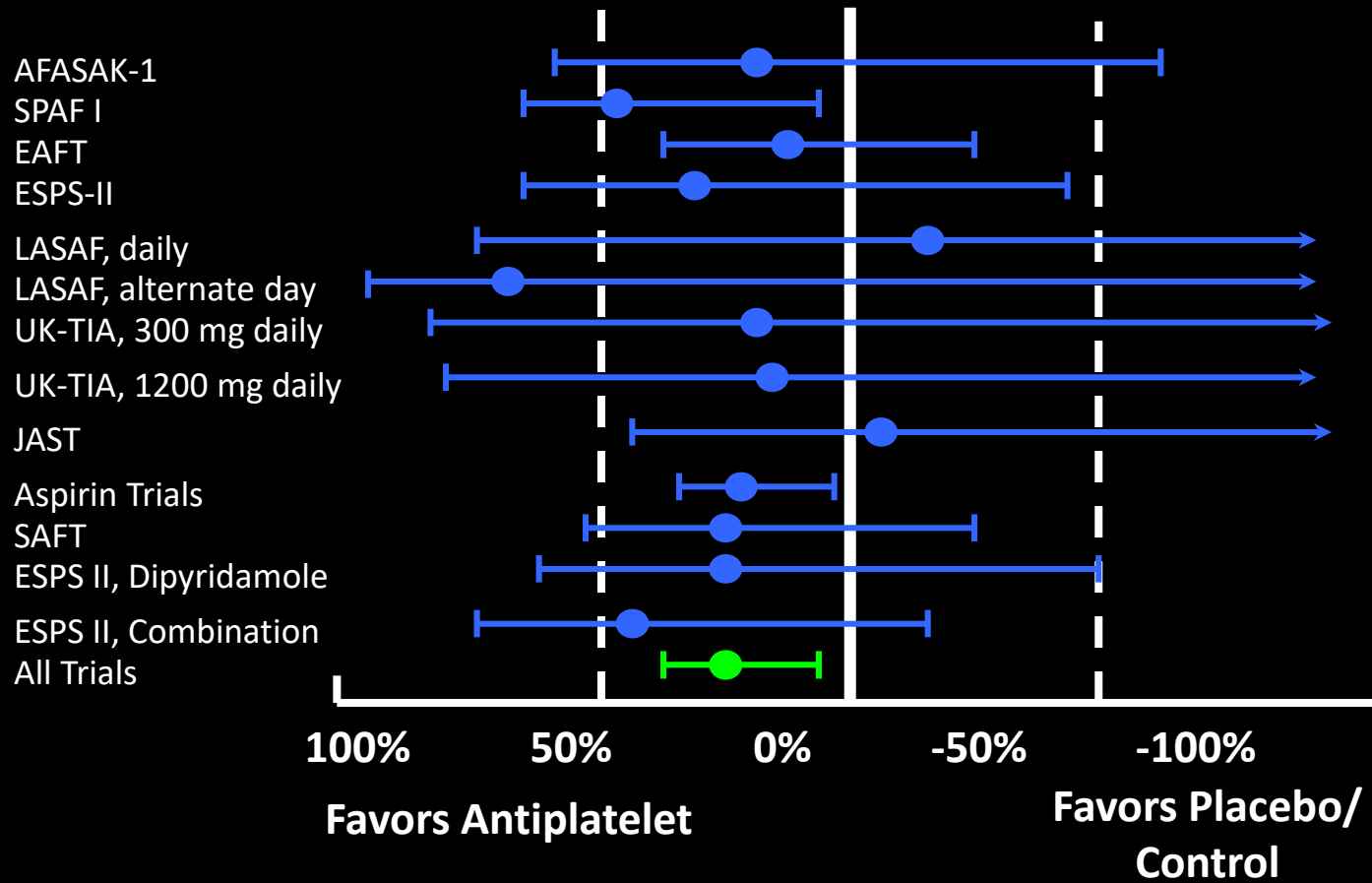
– *Arch Intern Med.* 1999;159(7):677-685. doi:10.1001/archinte.159.7.677

- Beware fallers with significant injury
 - Major head injury with proven SDH
 - Major bruising resulting in surgery

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Aspirin vs Placebo in Stroke Prevention in AF

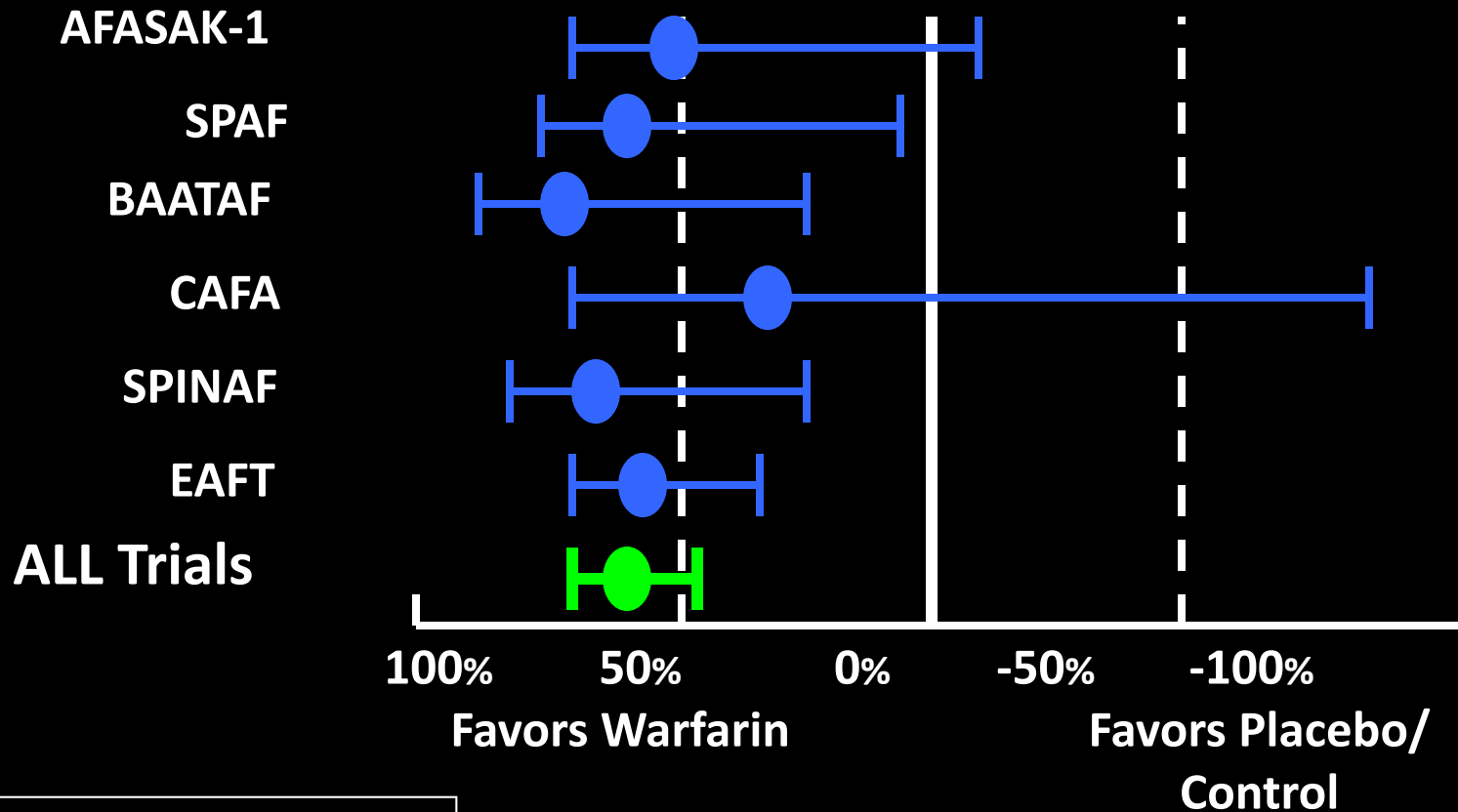


Antiplatelet therapy reduces incidence of stroke by about 22%

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Warfarin vs Placebo in Stroke Prevention in AF



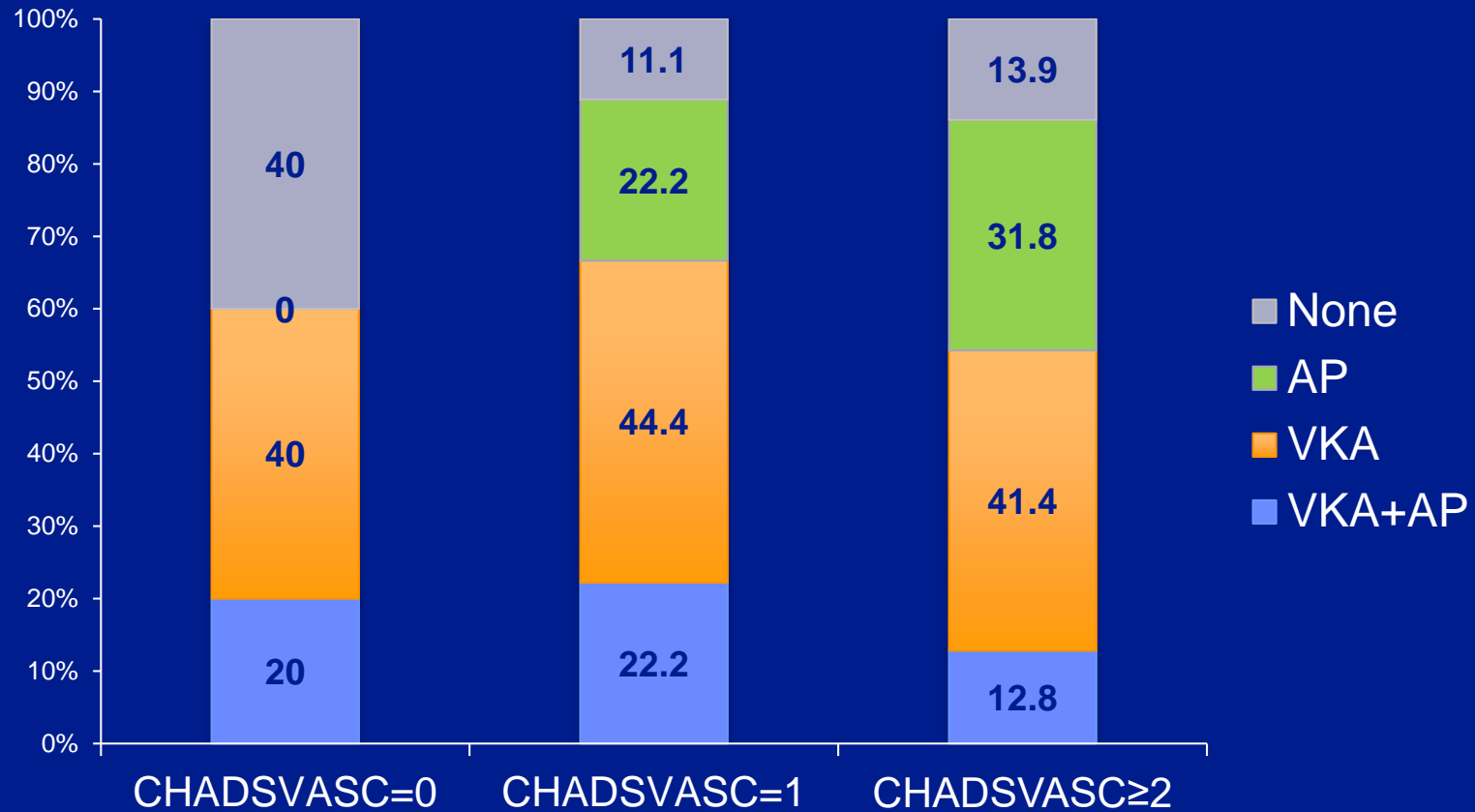
Warfarin reduces incidence of stroke by about 64%



Global Anticoagulant Registry in the FIELD (GARFIELD)

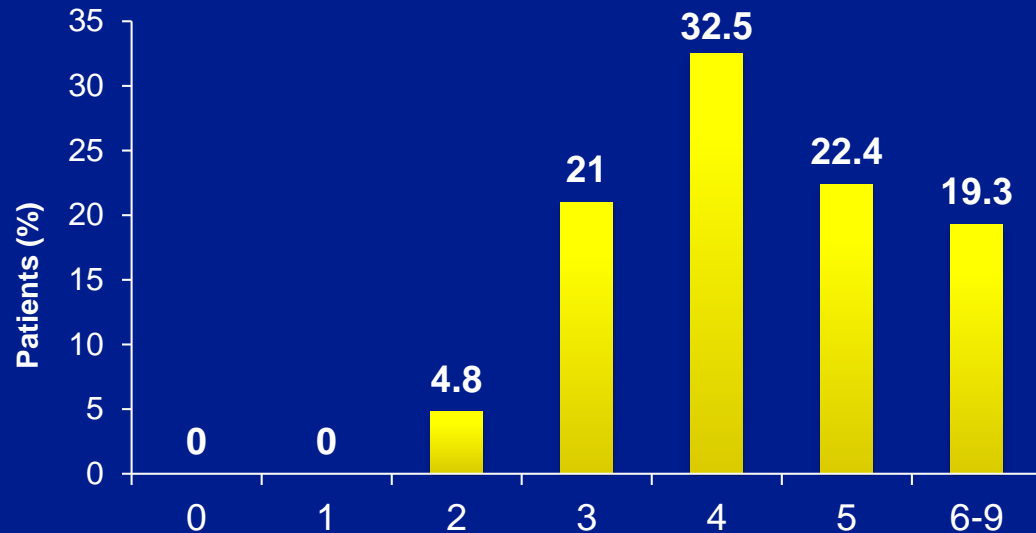
**GARFIELD is supported by an unrestricted
research grant from Bayer Pharma AG to the
Thrombosis Research Institute**

Antithrombotic use according to CHA₂DS₂VASc score

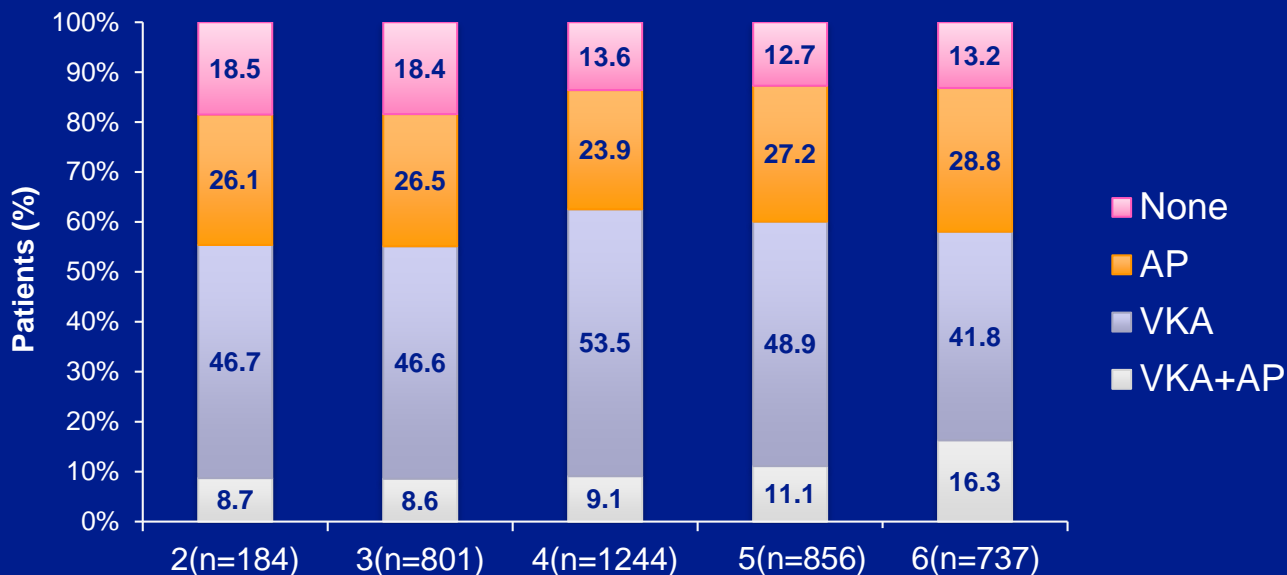


GARFIELD-AF Cohort 1 :

Outcomes in elderly newly diagnosed AF patients (1)

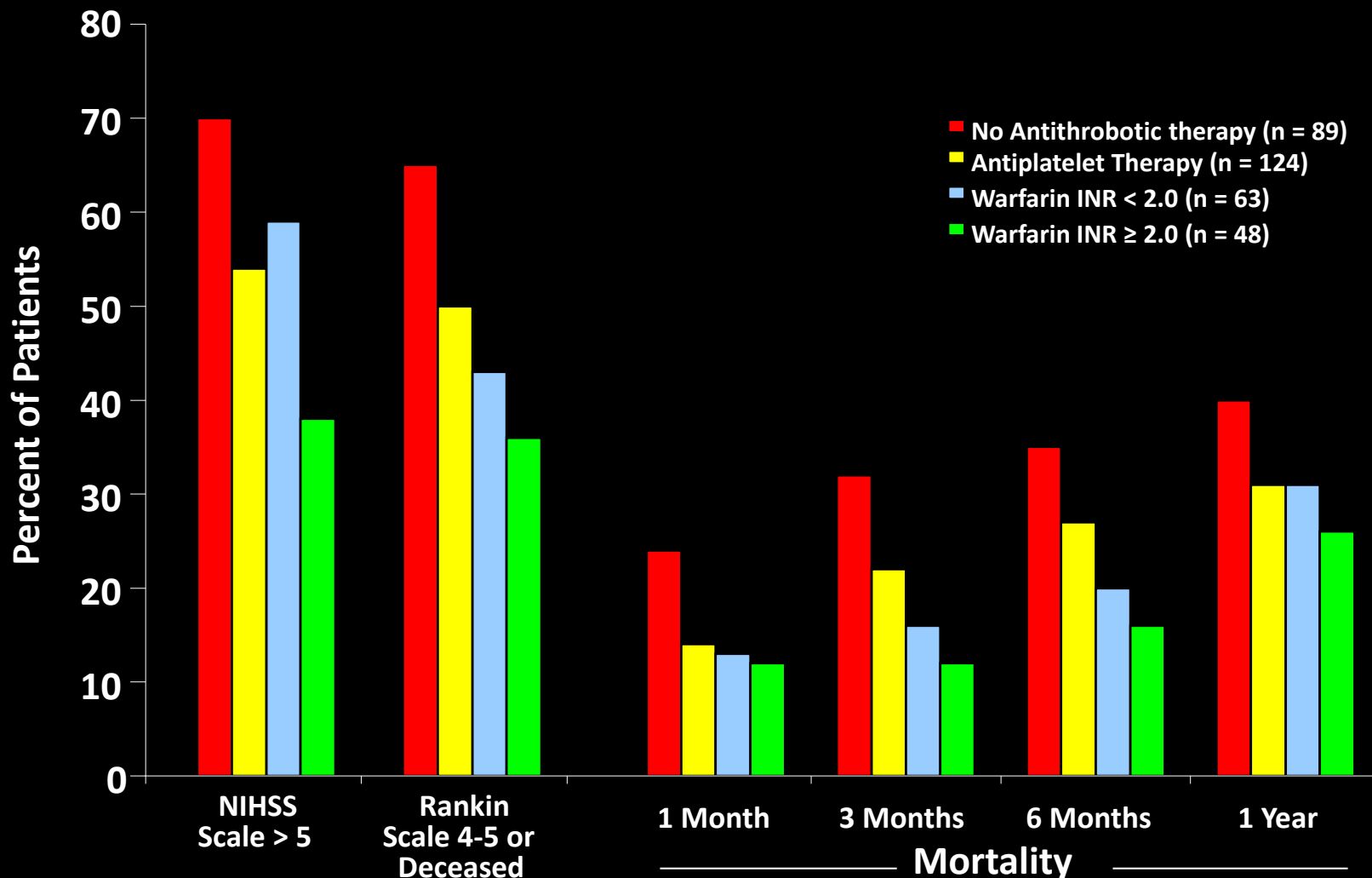


- 36.2% of patients in Cohort 1 were 75 y.o. or older (n=3813)
- $\frac{3}{4}$ of this population had CHA₂DS₂-VASc ≥ 4



Effective Anticoagulation – Stroke Severity and Survival: National Acute Stroke Israeli Survey

Patients with AF admitted with acute ischemic stroke or transient ischemic attack

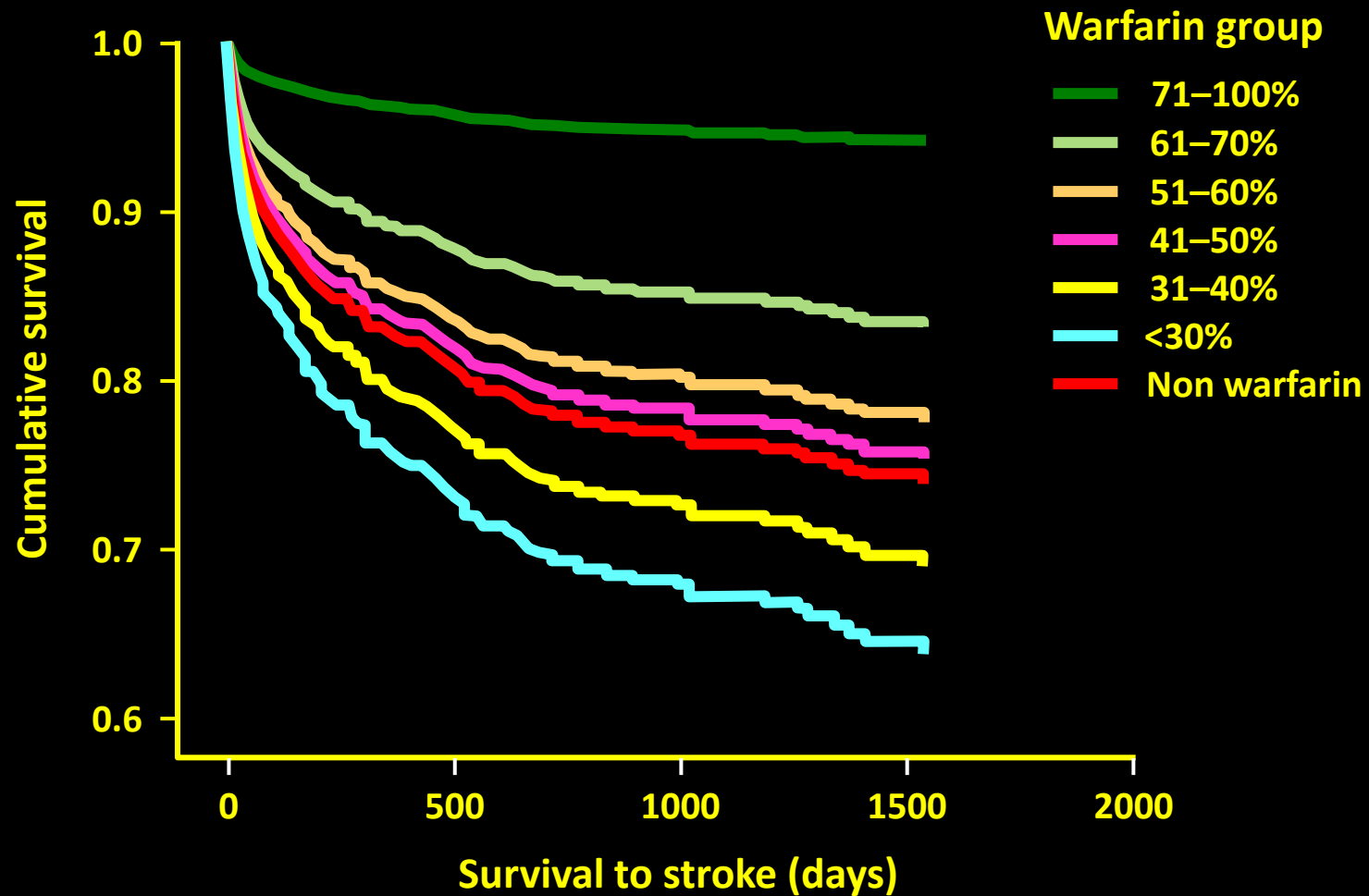


NIHSS Scale: National Institutes of Health stroke scale (stroke severity on admission)

Rankin Scale: Functional disability at discharge

Schwammenthal Y, et al. *Am J Cardiol.* 2010;105:411-416.

Time in therapeutic range (TTR) matters



The perfect anticoagulant

- Effective
- Oral
- Fast onset of action
- Short half life
- Predictable pharmacokinetics
- No drug/food interactions
- Fully reversible

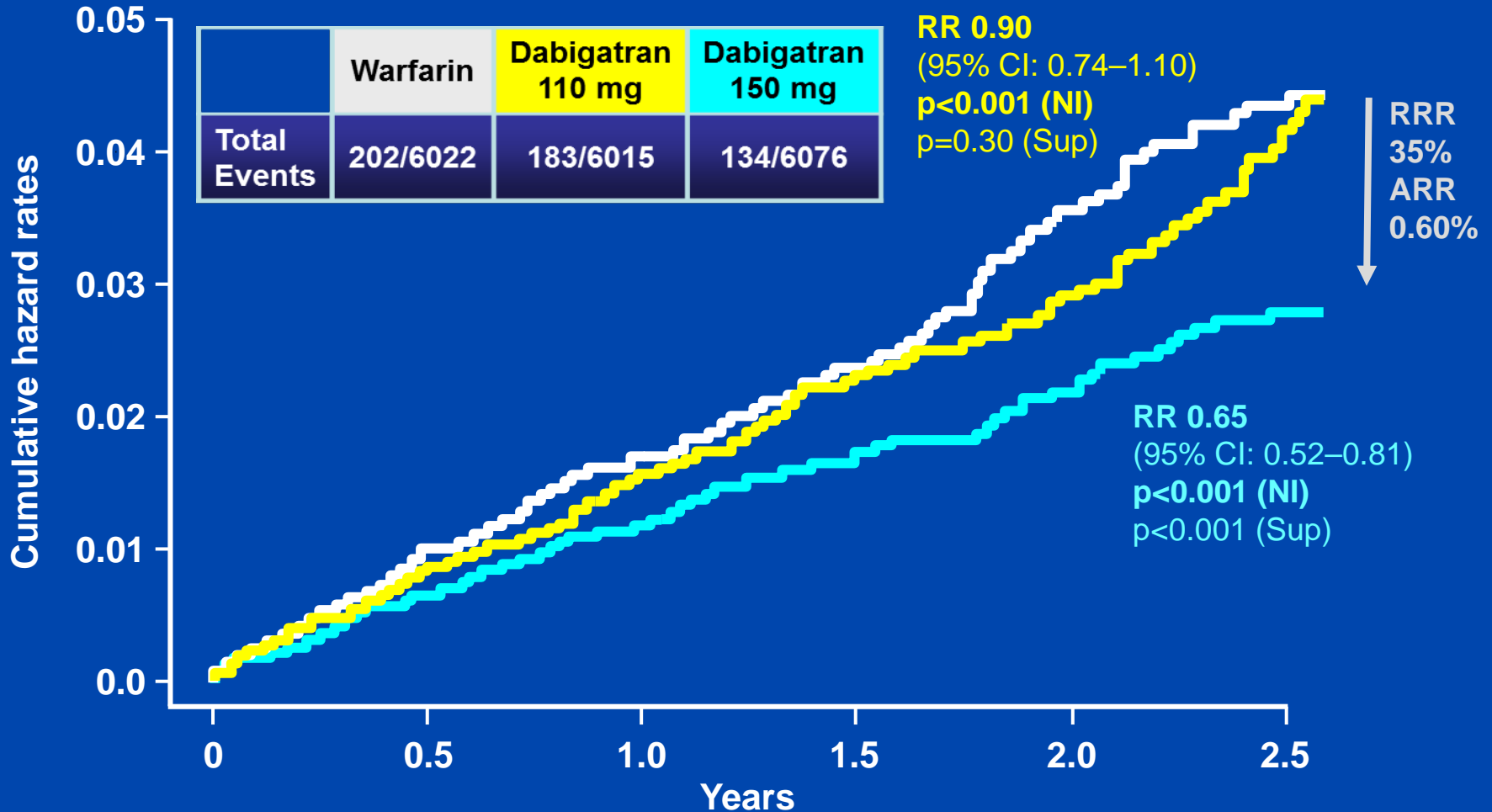
- Do the NOACs fulfill these criteria?

Non Vitamin K Oral Anticoagulant Use
for
Stroke Prevention in AF



"I'm going to prescribe something that works like aspirin but costs much, much more."

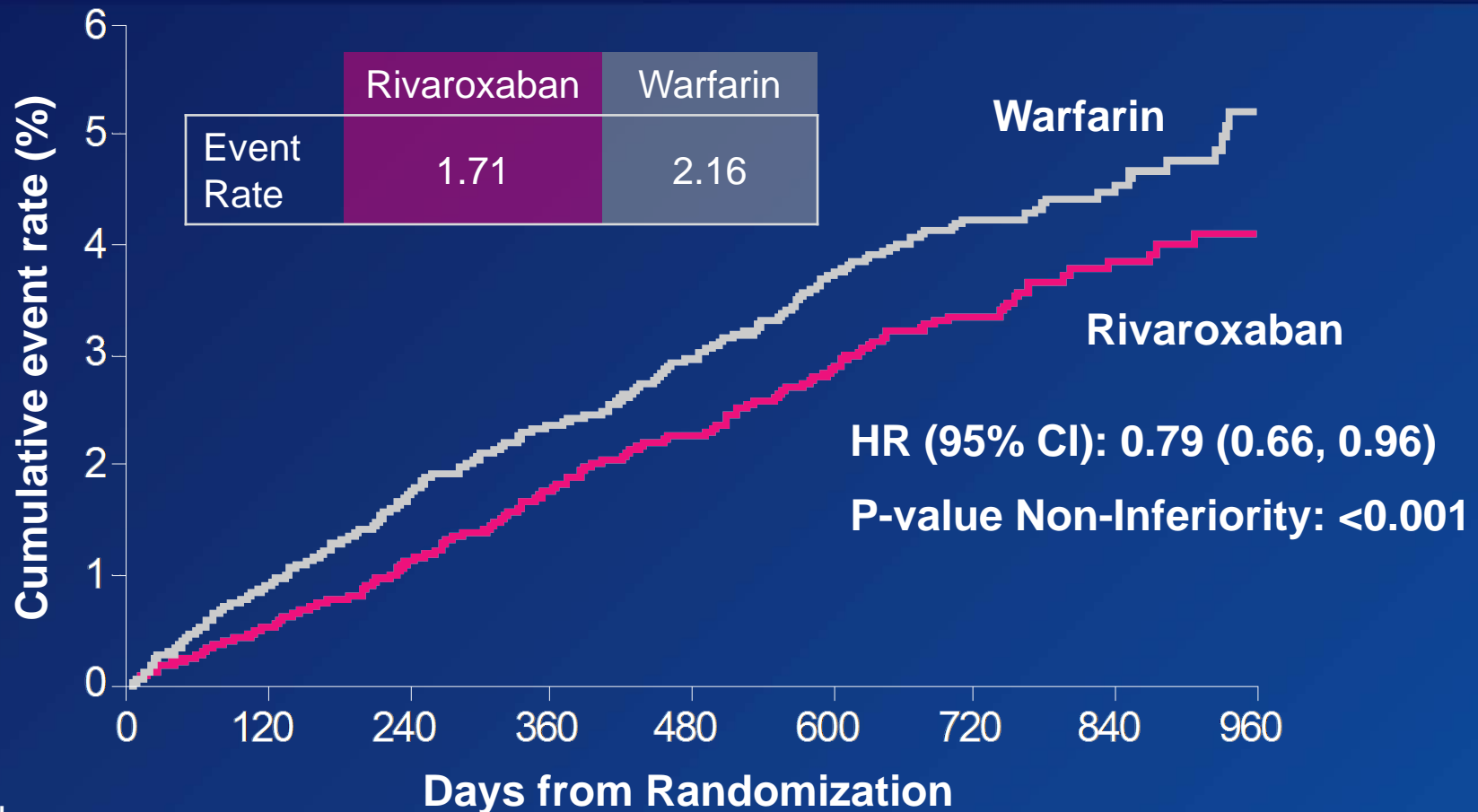
How does Pradaxa® compare to warfarin? Time to first stroke / SSE



ARR, absolute risk reduction; RR, relative risk; CI, confidence interval; NI, non-inferior; Sup, superior

Primary Efficacy Outcome

Stroke and non-CNS Embolism



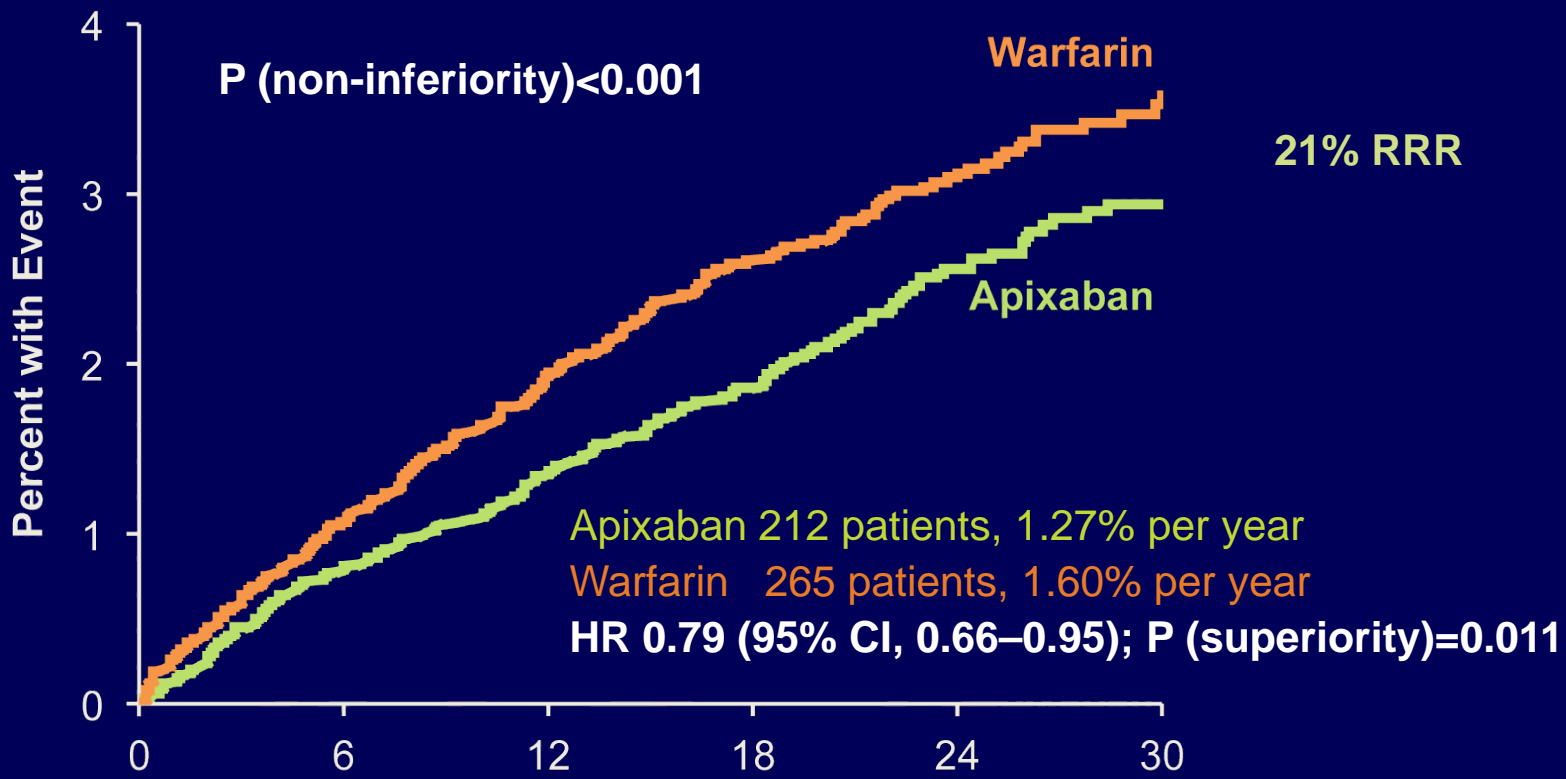
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
 Based on Protocol Compliant on Treatment Population

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk

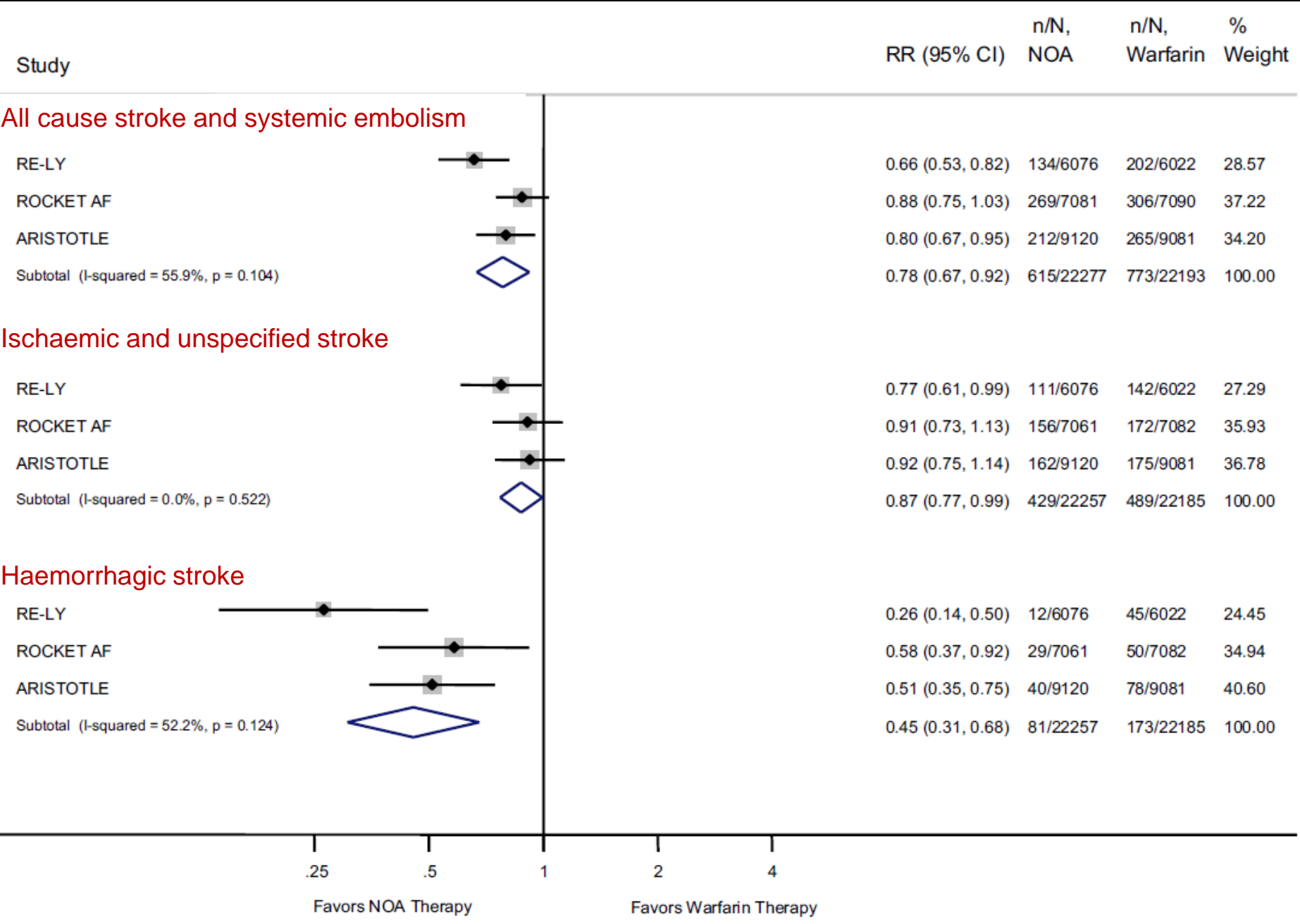
	0	6	12	18	24	30
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

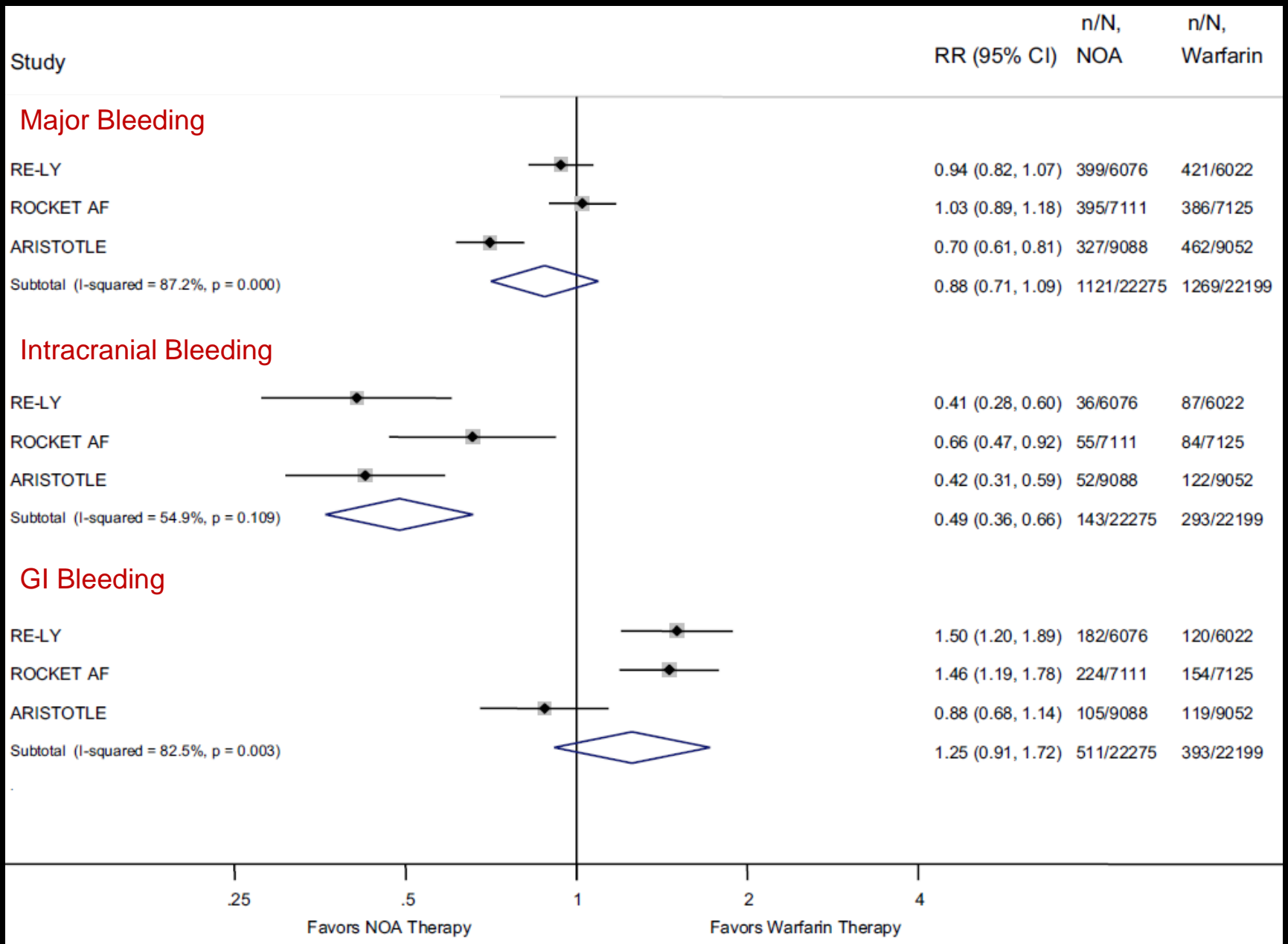
Summary of results

ARISTOTLE	RE-LY	ROCKET-AF
<p>Apixaban superior to warfarin:</p> <ul style="list-style-type: none"> • In preventing stroke or systemic embolism • In causing less bleeding including ICH • In reducing mortality. 	<p>Dabigatran 150mg superior to warfarin:</p> <ul style="list-style-type: none"> • In preventing stroke or systemic embolism • In reducing ischaemic stroke • In causing less ICH <p>Major bleeding rates are similar</p> <p>Causes more GI bleed</p>	<p>Rivaroxaban non-inferior to warfarin: (superiority with on-treatment analysis)</p> <ul style="list-style-type: none"> • In preventing stroke or systemic embolism <p>Similar rate of bleeding</p> <p>Causes less ICH</p>
	<p>Dabigatran 110mg non-inferior to warfarin:</p> <p>In preventing stroke or systemic embolism</p> <p>Causes less major bleeding</p> <p>Causes less ICH</p>	

Meta - analysis

- 3 major trials
- Total of 44,563 patients
- 22,327 to new oral anticoagulants and 22,236 to warfarin.
- Mean follow-up ranged from 657 to 730 days
- Average age ranged from 70 to 73 years.
- Women 35% to 40%
- Mean time in the therapeutic range of warfarin ranged from 55% to 64%.





Meta-analysis conclusions

- New oral anticoagulants are more efficacious than warfarin for the prevention of stroke and systemic embolism in patients with AF.
- With a decreased risk for intracranial bleeding, they appear to have a favorable safety profile, making them promising alternatives to warfarin

Indications and Dosing

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Prevention of VTE post THR/TKR	110mg bd	2.5mg bd		10mg od
Prevention of CVA in AF	150mg bd (110mg bd)	5mg bd (2.5mg bd)	60mg od	20mg od
Treatment of acute VTE	150mg bd	10mg bd for 7/7 5mg bd	60mg od	15mg bd for 3/52 20mg od

Renal function

Anticoagulant	Creatinine clearance (ml/min)		
	30-50	30-15	<15
Apixaban	5mg bd	2.5mg bd	AVOID
Dabigatran	150mg bd (110mg bd)	AVOID	
Edoxaban	60mg	30mg	AVOID
Rivaroxaban	15mg od	15mg od	AVOID

How do NOACs affect the
coagulation screen?

Coagulation tests with Anticoagulant Drugs

Test	UFH	LMWH	Warfarin	Rivaroxaban	Apixaban	Dabigatran
PT	-	-	↑↑↑	↑/-	-/↑	-/↑
APTT	↑↑↑	-/↑	↑	-/↑	-/↑	↑↑↑
Fibrinogen	-	-	-	-	-	-
Thrombin Time	↑↑↑	↑	-	-	-	↑↑↑
Anti-Xa	↑	↑↑↑	-	↑↑↑	↑↑↑	-
Haemoclot	↑↑	↑	-	-	-	↑↑↑

Switching from one
anticoagulant to another

Switching from warfarin to NOAC

- Apixaban
 - Wait till INR < 2.0
- Dabigatran
 - Wait till INR < 2.0
- Edoxaban
 - Wait till INR < 2.5
- Rivaroxaban
 - Wait till INR < 3.0 AF
 - Wait till INR < 2.5 DVT, PE

Emergency Surgery and Bleeding

Warfarin

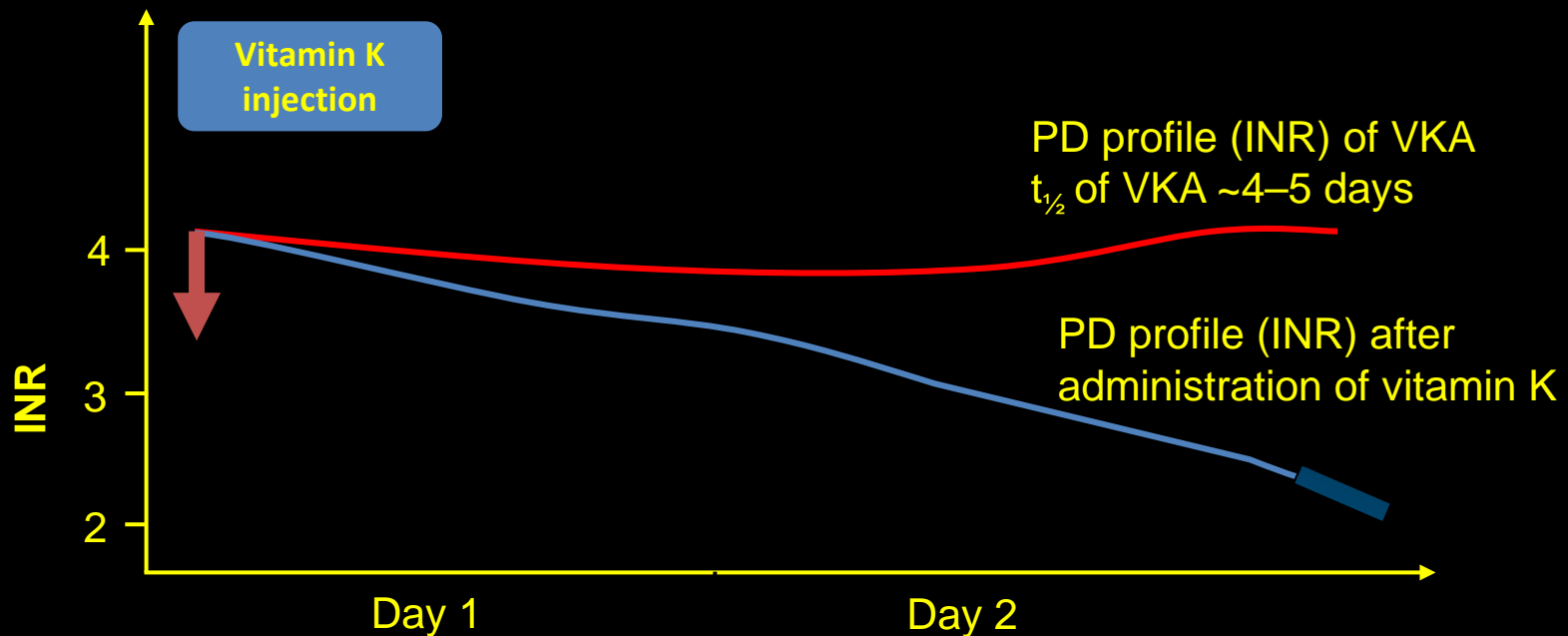
- Vitamin K
 - IV 6 hours
 - PO 24 hours
- Prothrombin complex concentrates (PCCs)
 - Factors II, VII, IX, X
 - Reversal within 30 minutes
- Can assess INR for effectiveness/safety

NOACs

- No specific reversal agent
- Well-adsorbed to activated charcoal
 - give within two hour of swallowing
- Dialysis
 - Dabigatran – yes
 - Rivaroxaban, apixaban – no
- General principles
 - Check coagulation screen
 - Assess effect
 - Check renal function
 - Assess half life
- Products
 - largely speculation/ based on non-clinical data
 - off-licence use; safety issues (thrombosis)

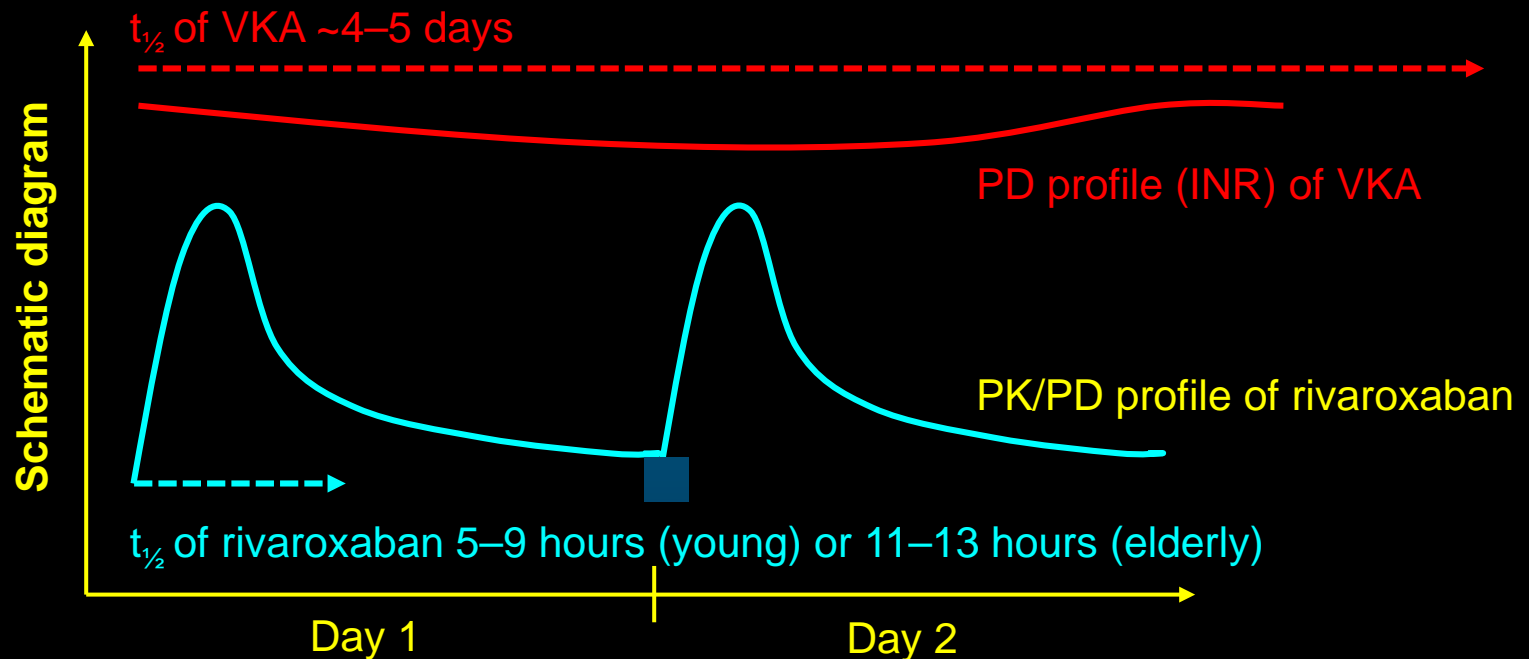
Vitamin K - no Immediate Effect on INR

- Schematic diagram showing effect of vitamin K on INR
- Vitamin K has a slow onset (>24 hours)¹
 - Vitamin K supports generation of normal, functioning clotting factors in the liver
 - Effectivity of INR normalization depending on VKA used (different half-lives; (from 9–11 hours for acenocoumarol, to 90–140 hours for phenprocoumon)^{1,2}



Emergencies in Anticoagulated Patients

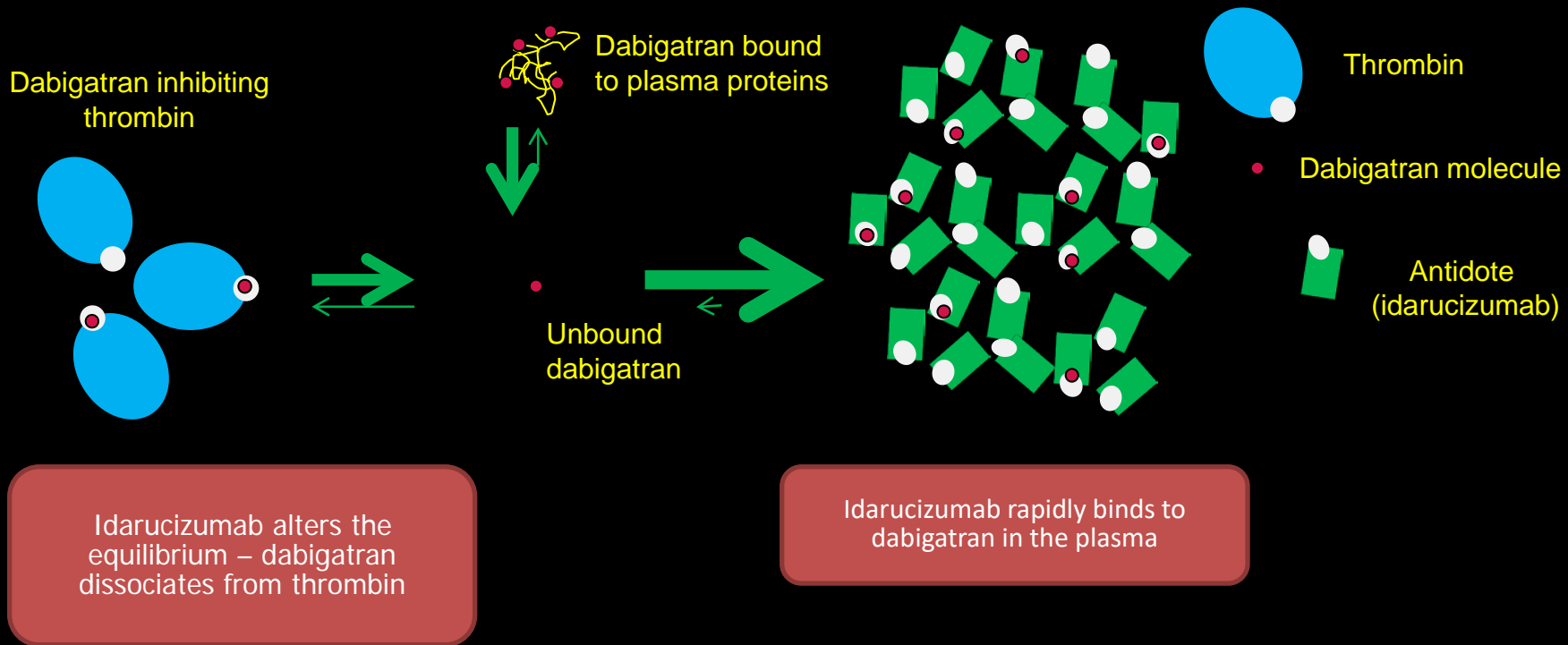
- Schematic diagram showing PK/PD characteristics of VKA and rivaroxaban
 - Reversal strategies may be required if action of drug is long and needs to be antagonized in emergency situations



Specific Reversal Agents for Non-VKA Oral Anticoagulants

Company	Compound	Reversal for:			Status
		Factor Xa inhibitor	Factor IIa inhibitor	LMWH/ fondaparinux	
Portola Pharmaceuticals	PRT064445/ (andexanet alfa)	Universal	No	Yes (antithrombin-mediated Factor Xa inhibition)	Phase II completed One phase III with apixaban completed; rivaroxaban and edoxaban - onngoing
Boehringer Ingelheim	BI 655075 (idarucizumab)	No	Specific for dabigatran	No	Phase I completed; ³ phase III started ⁴
Perosphere, Inc.	PER977 (aripazine)	Universal	Universal	Universal	Phase I completed ⁵

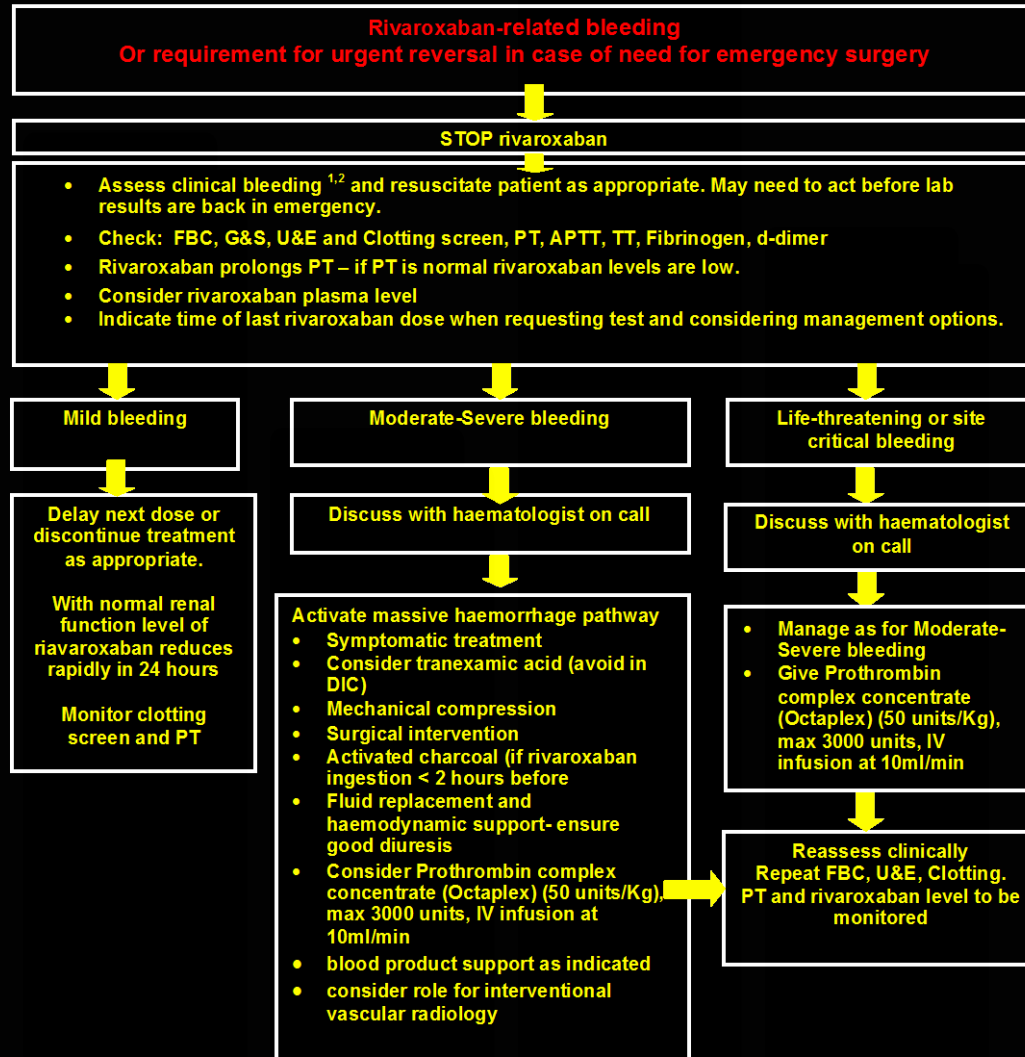
Idarucizumab mode of action



Guideline for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor with a half life of 7-11 hours and mostly renal 66% excretion.

There is no licensed reversal agent for rivaroxaban.



¹ Moderate to Severe bleeding: - reduction in Hb \geq 2gd/L, transfusion of \geq 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).

² Life-threatening bleeding: – symptomatic intracranial bleed, reduction in Hb \geq 5gd/L, transfusion of \geq 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

Pros

- Predictable anticoagulation response
- Absence of food interactions, and limited drug interactions
- Convenience
 - No need for monitoring
 - No need for frequent dose adjustment
- Rapid onset of action and relatively short half-life periods
 - Convenient around procedures; no need for bridging

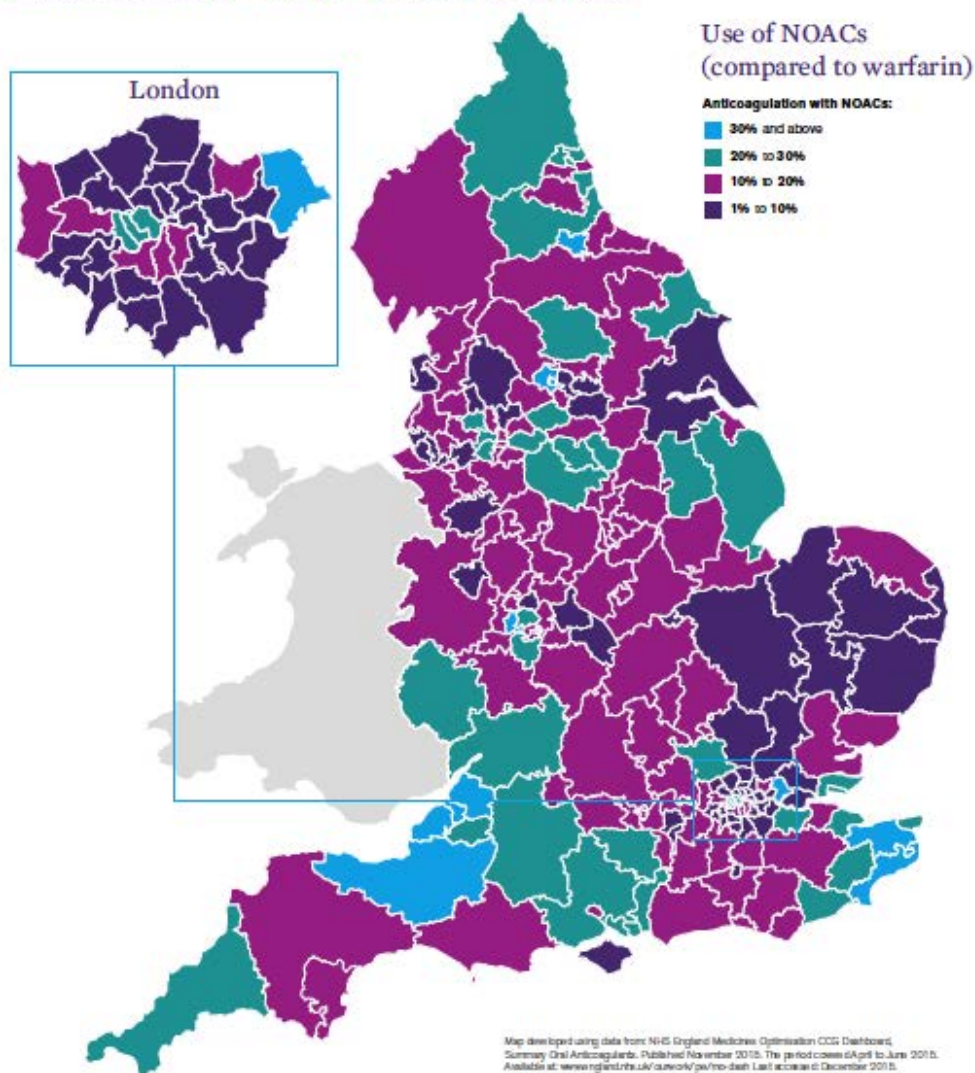
Cons

- Reversal?
- Missed dose can increase the risk of stroke
- No routine coagulation monitoring may facilitate non-compliance
- No coagulation assay easily available to precisely measure anticoagulation effect
- Cost
- Not advisable in CrCl<30

Practical Points

- Patient education is important
- Compliance
- Missed doses

Use of Novel Oral Anticoagulants (NOACs) across Clinical Commissioning Groups (CCGs) in England



NOAC uptake is symptomatic of local variations in AF management and the need to provide all patients high quality anticoagulation.



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

NICE Quality Standards

- **Statement 1**
 - Adults with non-valvular atrial fibrillation and a CHA₂DS₂-VASc stroke risk score of 2 or above are offered anticoagulation
- **Statement 2**
 - Adults with atrial fibrillation are not prescribed aspirin monotherapy for stroke prevention
- **Statement 3**
 - Adults with atrial fibrillation who are prescribed anticoagulation discuss the options with their healthcare professional at least once a year.
- **Statement 4**
 - Adults with atrial fibrillation taking a vitamin K antagonist who have poor anticoagulation control have their anticoagulation reassessed
- **Statement 5**
 - Adults with atrial fibrillation whose treatment fails to control their symptoms are referred for specialised management within 4 weeks
- **Statement 6 (Developmental)**
 - Adults with atrial fibrillation on long term vitamin K antagonist therapy are supported to self-manage with a coagulometer

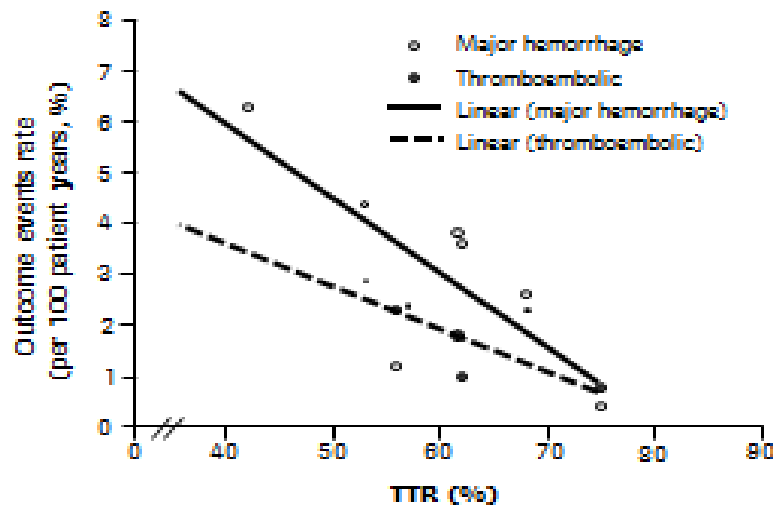
Patient self Testing/Management



- Decreased number of thromboembolic events and overall mortality without increase in bleeding
- TTR up to 85%

Patient self-testing

Improves TTR, reduces rate of adverse events



Adapted from Wan et al (2008)

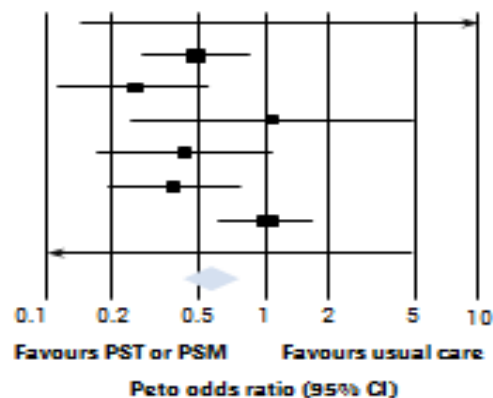
- PST improve quality of oral anticoagulation management
 - 55% reduction in thromboembolic events¹
 - Reduction in major hemorrhage¹
 - Reduction in mortality²
 - Frequent warfarin monitoring increases TTR – weekly 85%
 - Higher TTR linked directly to fewer adverse events³

1. Heneghan et al (2008). *Lancet* 387:404-411
2. Bloomfield et al (2011). *Ann Int Med* 154:472-482
3. Wan et al (2008). *Circulation* 118:7-91

Patient self-testing/management *Reduces major thromboembolic events*

Meta-analysis: major thromboembolic events in PST/PSM versus usual care

Study, year	Events/Total, n/n	Events/Total, n/n
<i>Long-term studies (≥ 12 mo)</i>	PST or PSM	Usual care
Sidhu and O'Kane (2001)	1/51	0/49
Körtke et al (2001 and 2007)	16/579	32/576
Menéndez-Jándula et al (2005)	4/368	20/368
Fitzmaurice et al (2005)	4/337	3/280
Siebenhofer et al (2008)	6/98	13/96
Eitz et al (2008)	14/470	21/295
Matchar et al (2010)	33/1,465	31/1,457
Soliman Hamad et al (2009)	0/28	1/28

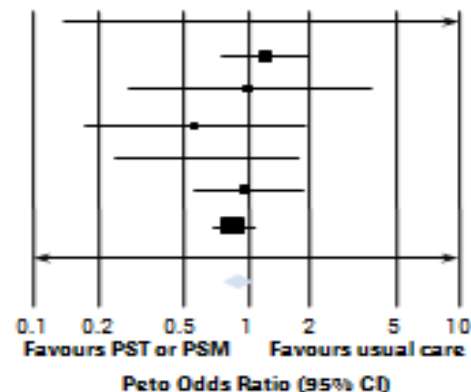


Adapted from Bloomfield et al (2011)

Self-testing/management *Reduces risk of serious bleeding*

Meta-analysis: major bleeding events in PST/PSM versus usual care

Study, year	Events/Total, n/n	
<i>Long-term studies (≥ 12 mo)</i>	PST or PSM	Usual care
Sidhu and O'Kane (2001)	1/51	0/49
Körtke et al (2001 and 2007)	42/579	34/578
Fitzmaurice et al (2005)	5/337	4/280
Menéndez-Jándula et al (2005)	4/368	7/369
Siebenhofer et al (2008)	7/99	10/96
Eitz et al (2008)	32/470	20/295
Matchar et al (2010)	180/1,465	189/1,457
Soliman Hamad et al (2009)	1/29	1/29



Adapted from Bloomfield et al (2011)

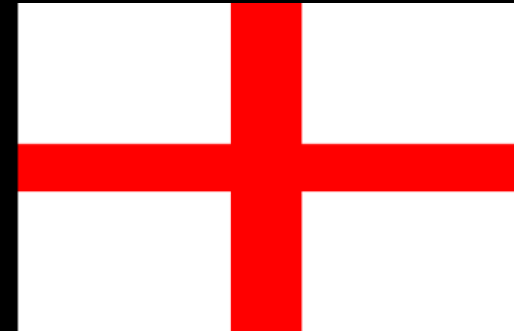
Patient Self Testing/Management

- For patients:
- greater convenience
- savings of time and transportation costs.
- control of their condition



Germany 20

- 81,859,000
- 800,000 on oral anticoagulants
- 160,000 self management¹ (20%)



England 3.4

- 62,262,000
- 500,000 on oral anticoagulants
- 17,000 self testing/management² (3.4%)

1. International Self Monitoring Association of Oral Anticoagulated Patients (ISMAAP) <http://www.ismaap.org/index.php?id=586> Accessed 25/6/12

2. Roche diagnostics - Personal communication

Costs Model

Year 1			
Hospital Based Service		Patient Self Management	
Initial consultation (consultant)	£150.00	Initial consultation (consultant)	£150.00
Initiation of warfarin consultation (nurse)	£50.00	Initiation of warfarin consultation (nurse)	£50.00
Subsequent consultations - during initiation		Subsequent consultations - during initiation	£150.00
		Capital cost for XS meter	£300.00
		Training patient on use of XS (Roche provide nurse)	
Daily time required to prepare reagents			
Cost of reagents per test, including QC	£19.00	Cost of reagents per test, including QC	£27.60
Time spend with patient testing	£200.00		
Time spend with patient dosing	£300.00		
Transportation costs for patients			
		Time spend on review of patient/XS unit 3 mo	£120.00
Cost of warfarin	£39.00	Cost of warfarin	£39.00
Total	£758.00	Total	£836.60

Costs Model

Year 2			
Hospital Based Service		Patient Self Management	
Initial consultation (consultant)		Initial consultation (consultant)	
Initiation of warfarin consultation (nurse)		Initiation of warfarin consultation (nurse)	
Subsequent consultations - during initiation		Subsequent consultations - during initiation	
		Capital cost for XS meter	
		Training patient on use of XS (Roche provide nurse)	
Daily time required to prepare reagents			
Cost of reagents per test, including QC	£19.00	Cost of reagents per test, including QC	£27.60
Time spend with patient testing	£200.00		
Time spend with patient dosing	£300.00		
Transportation costs for patients			
		Time spend on review of patient/XS unit 6 mc	£60.00
Cost of warfarin	£39.00	Cost of warfarin	£39.00
Total	£558.00	Total	£126.60

NICE Quality Standards+1

- **Statement A**
 - Find AF but don't call it screening and using simple ECG acquisition devices
- **Statement 1**
 - Adults with non-valvular atrial fibrillation and a CHA₂DS₂-VASc stroke risk score of 2 or above are offered anticoagulation
- **Statement 2**
 - Adults with atrial fibrillation are not prescribed aspirin monotherapy for stroke prevention
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- **Statement 5**
- **Statement 6 (Developmental)**
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6 Lessons in AF

1. AF is there is you know where to look...

...Just take the pulse, don't need to rewrite the book

2. Just anticoagulate them all, apart from the healthy

That keeps the patient well and the healthy economy wealthy

3. Check for those still taking the little useless Aspirin...

Give them warfarin or a NOAC and make it long lastin'

4. Let the patient choose their modality of treatment...

They will know best and what is right and what's decent

5. Don't let bleeding ruin the day...

Use HASBLED to show how to keep it at bay

6. Falling is terrible it can give you a bump

But a stroke is even worse it gives you the hump

Thank you for your attention

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