# Let's Talk Clots – South West Conference 2018

**Awarded 3 CPD Points from the Federation of the Royal Colleges of Physicians**

Wednesday 2nd May 2018

Bristol & Bath Science Park, Dirac Crescent, Emersons Green, Bristol, BS16 7FR

Endorsed by

## Faculty Biographies

**CHAIR – Mr Yousaf Ahmad - Chief Pharmacists, Care UK, NHS England**

*Yousaf is the Chief Pharmacist within Care UK which is the largest healthcare partner to NHS England covering Primary, Secondary, Health in Justice and Residential Care settings.*

*He is responsible for the management of all aspects of pharmacy services: including the provision of medicines information, formulary management, pharmaceutical procurement, distribution, over labelling activities and extemporaneous dispensing.*

*His expertise includes establishing policy and governance systems designed to deliver safe, effective and efficient medicines management practices.*

*As a key pharmacy leader, Yousaf is instrumental in leading the development and implementation of strategic plans for pharmaceutical services and for ensuring the development of a progressive and responsive service within a robust clinical governance framework. As a Lead pharmacist for NHS Scotland until 2016, Yousaf led on providing specialist clinical knowledge to analyse complex patient information and ensure optimal clinical outcomes. From participating in patient care ward rounds, holding clinical responsibility for high specialised units, providing medicine counselling to patients and families, designing workforce strategies to teaching and lecturing to pharmacy and non-pharmacy personnel and leading research projects.*

*Having also worked internationally in previous roles, Yousaf has gained a wealth of experience in optimising pharmaceutical clinical care across NHS and non-NHS services which led to the implementation of robust patient pharmaceutical management and outcomes.*

*His leadership has also involved participating in medicine use evaluation, protocol management and medicine research, sitting on clinical governance committees to provide recommendations pertaining to medication use and processes, including NICE Adoption and Impact Committee. Yousaf is a committee member at The Royal Pharmaceutical Society and a member for the editorial board for Pharmacy in Practice.*

**DR JOSEPHINE CROWE**

*Dr Crowe is a Consultant Haematologist at the Bath Royal United Hospital. Most recently she has been lead clinician on a regional initiative to optimise anticoagulation management across primary and community care in collaboration with secondary care specialists.*

**NATHAN JONES – ANTICOAGULATION PHARMACIST, BATH RUH**

*Nathan is a specialist pharmacist who has been working at the RUH for the past year as part of a multidisciplinary anticoagulation team. Since being in post he has been involved with the setting up of a cancer associated thrombosis telephone clinic, which was presented at the 2018 British Society of Haematology annual conference in Liverpool, piloting new models for anticoagulation management in primary care, optimising peri-procedural management of anticoagulation, working as part of a multidisciplinary thrombosis clinic and providing education and training to both healthcare professionals and medical/pharmacy undergraduates.*

**SUE BACON**

*Sue is a Nurse Specialist in thrombosis and anticoagulation and the Lead Anticoagulation Nurse with North Bristol NHS Trust.*

*With extensive experience in thrombosis service development, service management and embedding patient-centric care, Sue is now responsible for managing services supporting North Bristol Trust to ensure the safe and appropriate management patients requiring anticoagulation therapy.*

**STEPHANE JAGLIN**

*Stephane qualified as a Doctor of Pharmacy in 1994 in Nantes (France) and moved to the UK in 1998 where he worked as a community pharmacist for 14 years. He transferred to the secondary care sector in 2009 as clinical pharmacist within a treatment centre providing elective procedures in major orthopaedic surgery, general surgery, gynaecology, ENT and ophthalmology specialties.*

*Stephane developed a particular interest in anticoagulation, especially postoperative Venous Thrombosis prevention and perioperative management of anti-thrombotic drugs. He created a thrombosis committee for the hospital of which he is the lead and is now heavily involved in the development of national policies for VTE prophylaxis and perioperative use of anti-thrombotic medicines.*

*Stephane became a Trustee of Thrombosis UK in 2017*

**DR KHALID KHAN**

*Consultant Cardiologist and general practitioner at the Wrexham Maelor Hospital (part of Betsi Cadwaladr University Health Board). Dr Khan is based in the acute cardiac, acute general medical and ED and OP setting of this centre seeing more than 250 patients per month.*

*With particular clinical interests within cardiology, Dr Khan heads up an award- winning arrhythmia service within the Health Board.*

*More broadly Dr Khan has an interest in service redesign and innovation and has won several national awards for this work*

**DR AMANDA CLARK**

*Dr Clark is a consultant at Bristol United Hospital Trust, specialising in haematology, haemophilia and leading a specialised clinic for clotting disorders.*

**PROFESSOR SIMON NOBLE**

*Simon is a Clinical Professor in Palliative Medicine at Cardiff University and Honorary Consultant at the Royal Gwent Hospital in Newport. His research interests are in the management of venous thromboembolism in advanced cancer, the anti-cancer effects of heparins and the quality of life associated with VTE. Simon is involved at a national level in the delivery of evidence-based thromboprophylaxis for hospitalised patients through the All Party Parliamentary Thrombosis Group and through his work as Chair of the All Wales Hospital Acquired Thrombosis (HAT) Prevention Steering Group. He currently sits on the NICE guideline development group for prevention of VTE in hospitalized patients.*

**PROFESSOR DAVID FITZMAURICE**

*Professor David Fitzmaurice is a GP and Professor of Cardiorespiratory Primary Care at The University of Warwick.*

*He has a longstanding research interest in cardiovascular disease, in particular oral anticoagulation management. Prof Fitzmaurice was one of the first GPs awarded an MRC Career Scientist Award based on this research enabling him to develop as one of the primary care research leaders of today.*

**This meeting has kindly been supported by device, pharmaceutical and healthcare companies. Some companies, including pharmaceutical companies, have purchased exhibition space and will have a presence of an exhibition stand in the exhibition area.**

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| | | |
|---|---|---|
| 08:30 – 09:00 | **Registration – Refreshments and access to exhibition** | |
| **Time** | **Presentation** | **Speaker** |
| 09:00 – 09:05 | Introduction and welcome | **Chair: Mr Yousaf Ahmad**<br>Chief Pharmacist Care UK |
| 09:05 – 09:30 | 'Optimisation of anticoagulation,' GP Pilot Project | **Dr Josephine Crowe** Consultant Haematologist<br>**Nathan Jones** Anticoagulation Pharmacist<br>Bath Royal United Hospital |
| 09:30 – 09:55 | Practical tips in initiating and maintaining an anticoagulation treatment | **Sue Bacon**<br>Nurse Specialist in thrombosis & anticoagulation & Lead Anticoagulation Nurse with North Bristol NHS Trust |
| 09:55 – 10:20 | VTE prevention and perioperative management of patients: following NICE 2018 guidance NG89 | **Stephane Jaglin**<br>Clinical Pharmacist |
| 10:20 – 10:45 | | |
| **Notes:** | | |
| 10:45 – 11:10 | Medico-legal challenges and issues | **Dr Khalid Khan** |

| | | |
|---|---|---|
| | | Consultant Cardiologist and Medico-Legal specialist, Wrexham Maelor Hospital |
| 11:10 – 11:35 | What's new in obstetrics prevention and management of thrombosis | **Dr Amanda Clark** University Hospitals Bristol NHS Trust |
| 11:35 – 12:00 | Cancer Associated Thrombosis | **Professor Simon Noble** Clinical Professor and Honorary Consultant in Palliative Medicine Royal Gwent & Cardiff University |
| 12:00 – 12:25 | Managing anticoagulation therapy for stroke prevention. -who cares wins | **Professor David Fitzmaurice** Professor of Cardio-respiratory Primary Care & National Lead for Centre for Anticoagulation Training, Warwick |
| 12:25 – 12:30 | Question and Answer session | **All speakers** |

**Notes:**

| | |
|---|---|
| 12:30 | Close of meeting – light lunch available |

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Royal United Hospitals Bath
NHS Foundation Trust

# Optimisation of Anticoagulation GP Pilot Project

Josephine Crowe – Consultant Haematologist
Nathan Jones – Anticoagulation Pharmacist
Sophie Didcott – Anticoagulation Nurse

Everyone Matters
Working Together
Making a Difference

# Overview

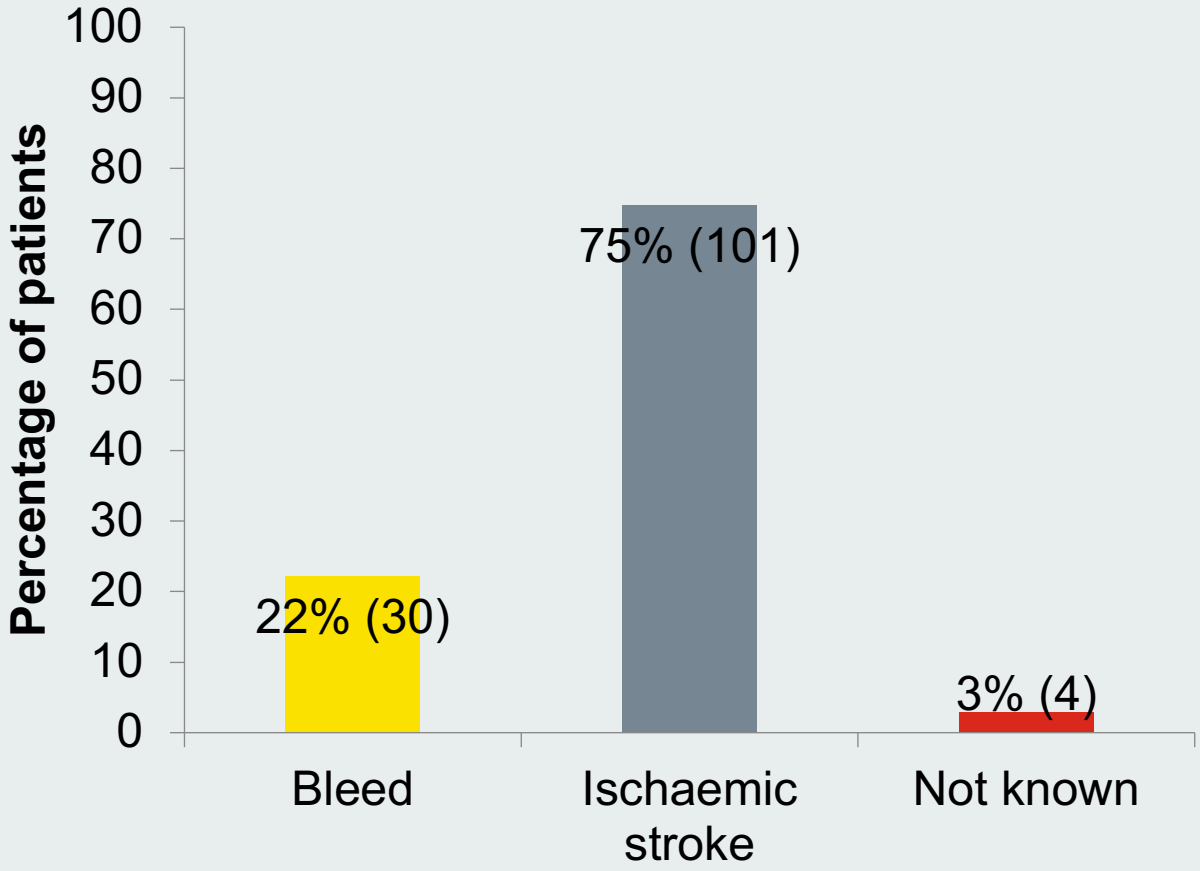
- Background – baseline data
- Overview of the GP pilot project
- Annual review
- Switching plans
- Project recruitment
- Results so far
- Conclusions and next steps

# Background

- For 2016 = **335** potentially preventable anticoagulation related harm events.
- Harm events in the community currently unknown.
- Data doesn't include harm for patients where INR is in range or where on the correct dose of DOAC etc.

# % of patients admitted with known AF presenting with either an ischaemic stroke or CNS bleed for 2016

- In total 135 patients with known AF were admitted to the RUH in 2016 with either an ischaemic stroke or CNS bleed.



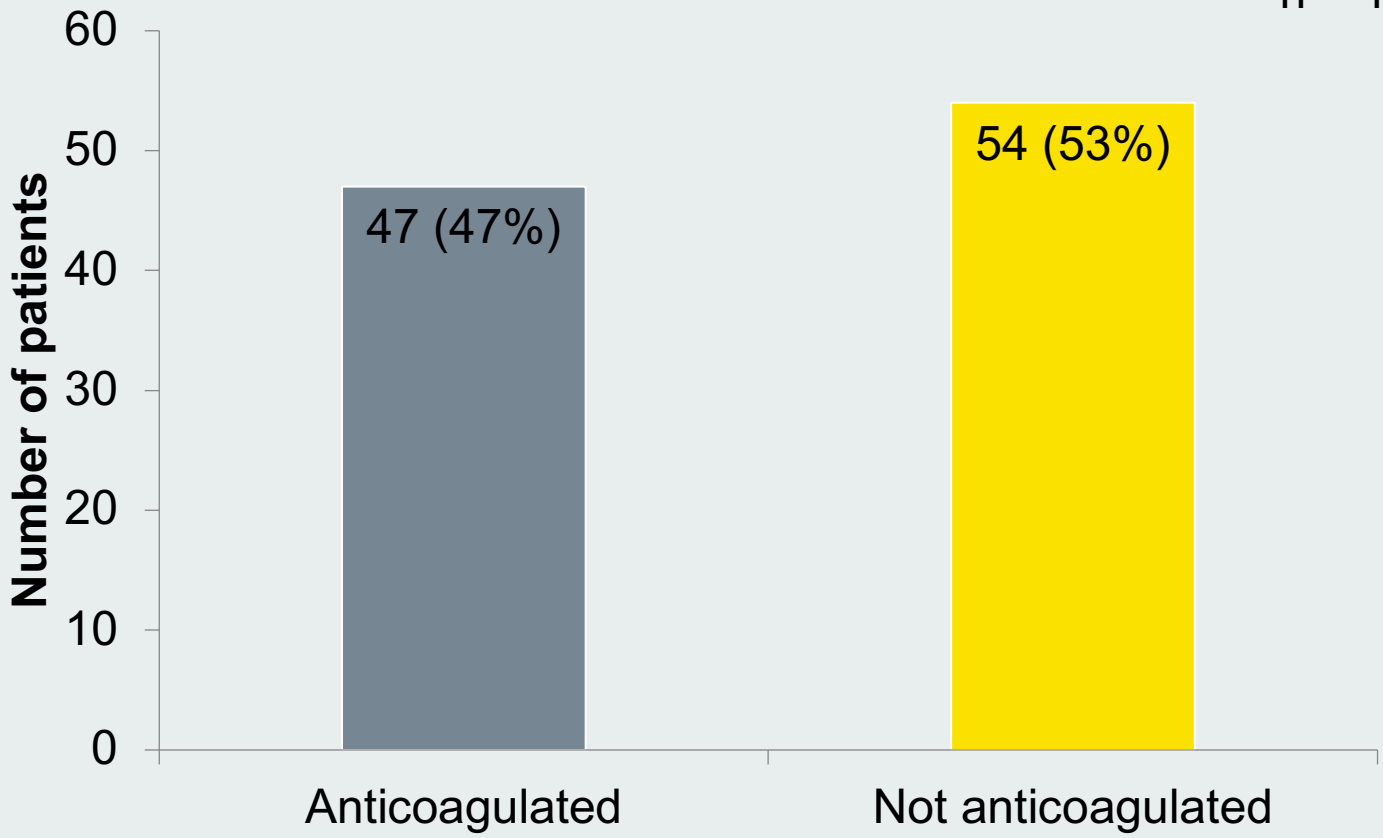
# Impact

For patients with known AF admitted with either an ischaemic or CNS bleed:

- **1575** = Total number of days spent at the RUH
- **29 days** = Average length of stay (LOS)
- **20%** of patients died within first 4 weeks.

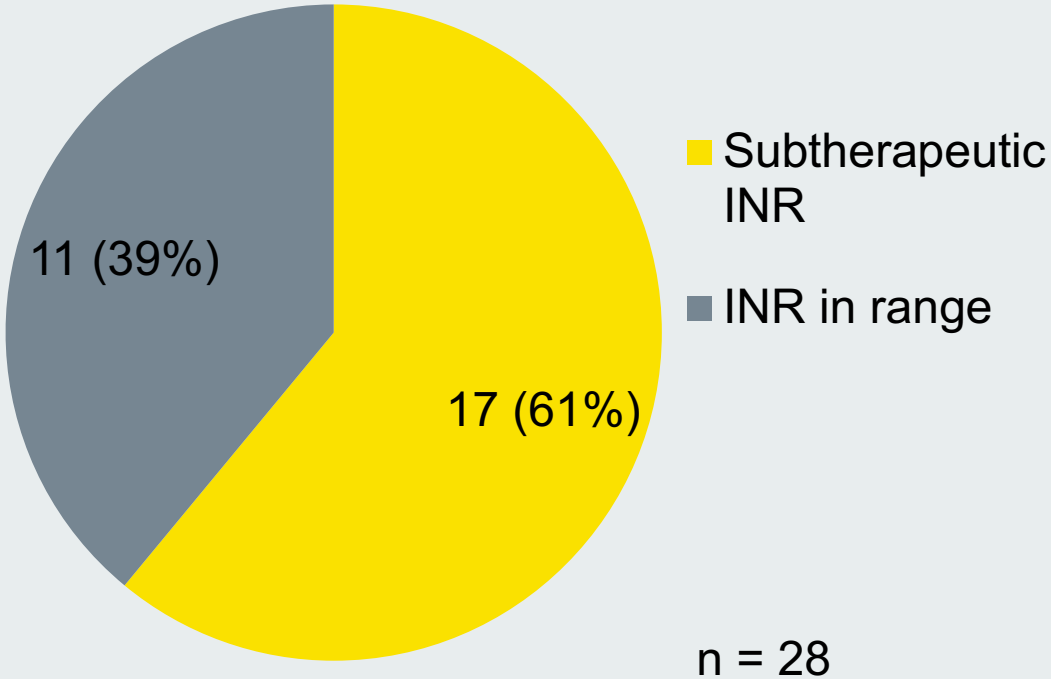
# No. patients diagnosed with an ischaemic stroke who were already on anticoagulation

n = 101



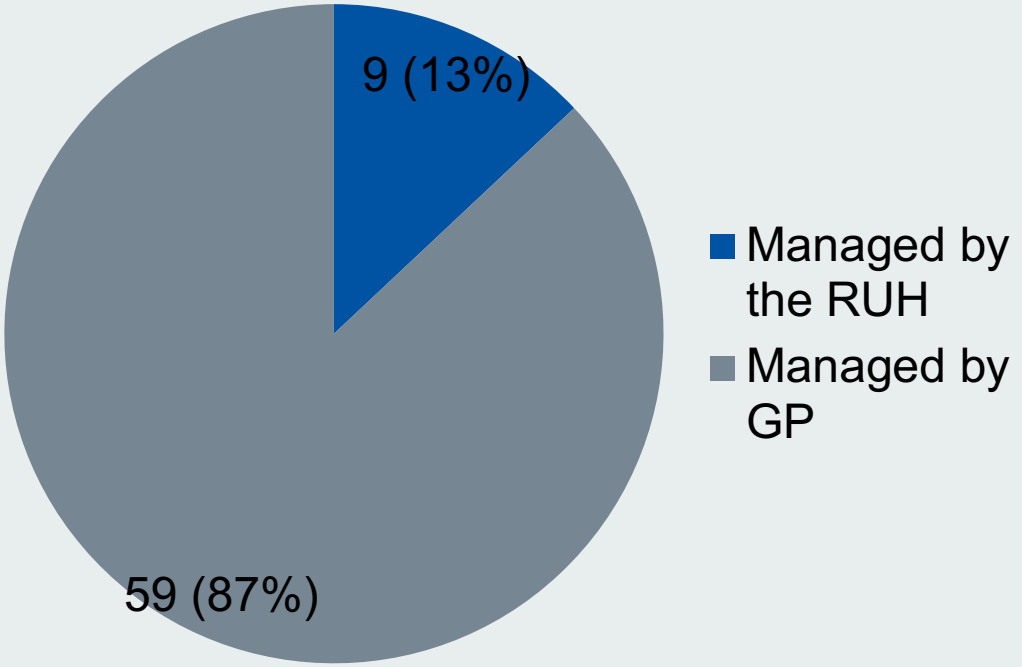
# Number of patients on warfarin admitted with an ischaemic stroke and sub therapeutic INR

- 17 patients with a sub therapeutic INR
- 1 patient (6%) managed by the RUH, 16 (94%) managed by GP



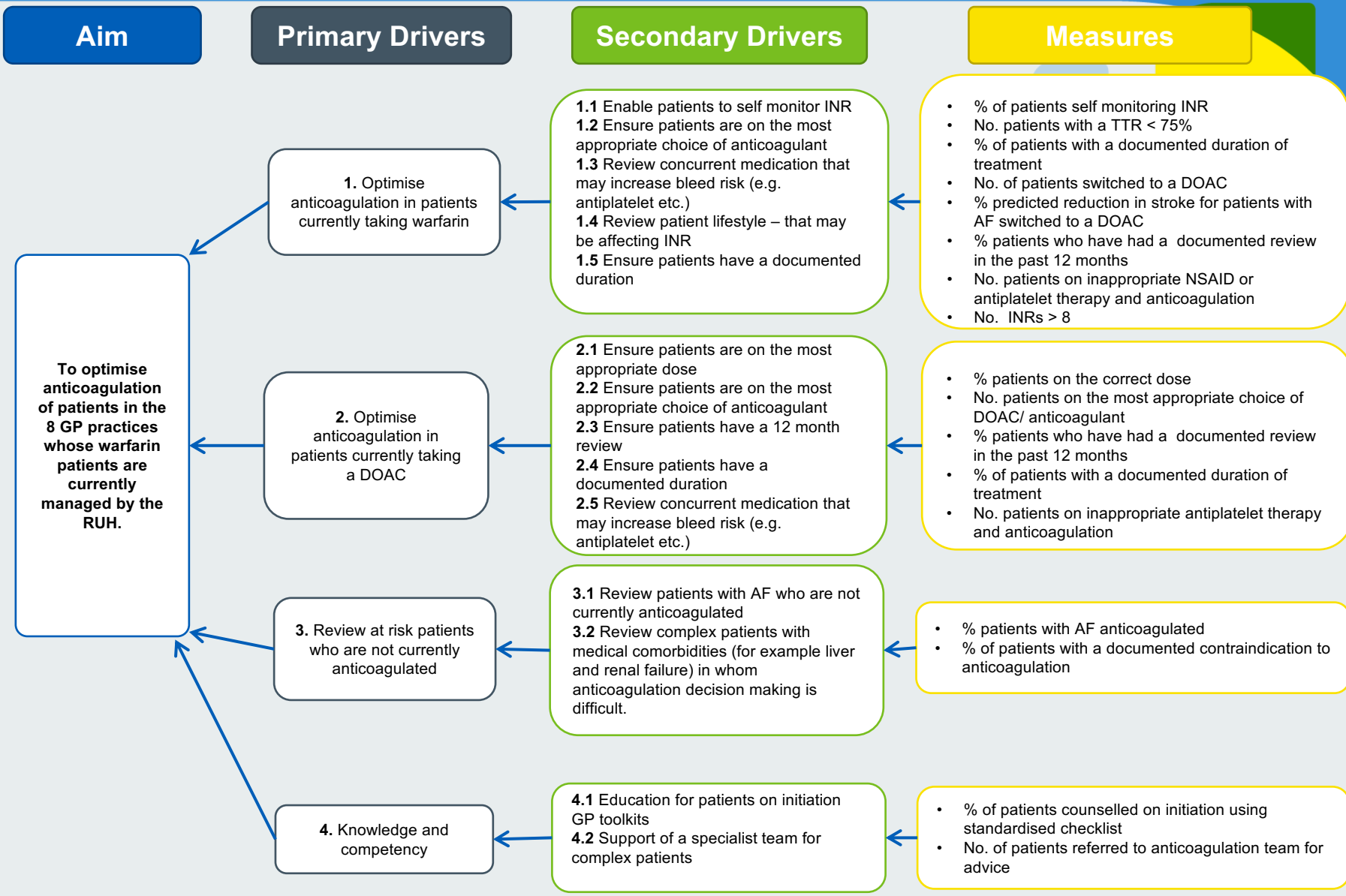
# Hospital Admissions over 12 month period (2016) due to INR > 8

- 68 cases of community INR>8 leading to/contributing to hospital admission in 2016
- Admission duration = **1 to 73 days**
- Average length of stay = **14.2 days**



# What can we change?

- **£1 million** spent on oral anticoagulation agents in BaNES (2016) – biggest increase in drug spend
- **£2 million** in avoidable admissions
- Need for a specialist service


Aim
Primary Drivers
Secondary Drivers
Measures
To optimise anticoagulation of patients in the 8 GP practices whose warfarin patients are currently managed by the RUH.
1. Optimise anticoagulation in patients currently taking warfarin
1.1 Enable patients to self monitor INR
1.2 Ensure patients are on the most appropriate choice of anticoagulant
1.3 Review concurrent medication that may increase bleed risk (e.g. antiplatelet etc.)
1.4 Review patient lifestyle – that may be affecting INR
1.5 Ensure patients have a documented duration
% of patients self monitoring INR
No. patients with a TTR < 75%
% of patients with a documented duration of treatment
No. of patients switched to a DOAC
% predicted reduction in stroke for patients with AF switched to a DOAC
% patients who have had a documented review in the past 12 months
No. patients on inappropriate NSAID or antiplatelet therapy and anticoagulation
No. INRs > 8
2. Optimise anticoagulation in patients currently taking a DOAC
2.1 Ensure patients are on the most appropriate dose
2.2 Ensure patients are on the most appropriate choice of anticoagulant
2.3 Ensure patients have a 12 month review
2.4 Ensure patients have a documented duration
2.5 Review concurrent medication that may increase bleed risk (e.g. antiplatelet etc.)
% patients on the correct dose
No. patients on the most appropriate choice of DOAC/ anticoagulant
% patients who have had a documented review in the past 12 months
% of patients with a documented duration of treatment
No. patients on inappropriate antiplatelet therapy and anticoagulation
3. Review at risk patients who are not currently anticoagulated
3.1 Review patients with AF who are not currently anticoagulated
3.2 Review complex patients with medical comorbidities (for example liver and renal failure) in whom anticoagulation decision making is difficult.
% patients with AF anticoagulated
% of patients with a documented contraindication to anticoagulation
4. Knowledge and competency
4.1 Education for patients on initiation GP toolkits
4.2 Support of a specialist team for complex patients
% of patients counselled on initiation using standardised checklist
No. of patients referred to anticoagulation team for advice

# Anticoagulation annual review

- Review indication for anticoagulation
- Reassess thromboembolic risk
- Assess bleeding risk factors
- Review duration of anticoagulation
- Patient education, information, and decision support
- Assess medication adherence
- Complications related to anticoagulation treatment (check for possible ADRs)
- Review of alternative anticoagulant strategies if applicable
- Medicines optimisation (ensure that anti-platelets not concomitantly prescribed unless there is a definite reason as recommended by a named specialist).

**London Clinical Networks. August 2016.**

**Warfarin**:

- Assessment and documentation of TTR
- Assessment of INRs that fall outside of the therapeutic range
- Review possibility of self-monitoring of INR if applicable


**DOACs**:

- Renal +/- liver function as indicated
- Weight
- Rivaroxaban – food intake
- Dose




# Switching plans

NHS
Royal United Hospitals Bath
NHS Foundation Trust

Anticoagulation Team
Royal United Hospital
Combe Park
Bath
BA1 3NG

Tel: 01225 825307

ruh-tr.AnticoagulationTeam@nhs.net
www.ruh.nhs.uk

Date

Patient Name:
Date of Birth:
MRN:
NHS number:

Dear NAME

**This plan is for patients who are being switched from warfarin to apixaban**

Apixaban is an example of a Direct Oral Anticoagulant (DOAC). These are an alternative group of drugs to warfarin, they are usually used for:

- Stroke prevention in Non-Valvular Atrial Fibrillation (AF)
- Treatment and Prevention of recurrent DVT and PE

Apixaban is also occasionally used for other indications.

**Advantages vs. disadvantages of taking apixaban instead of warfarin**

| Advantages of taking apixaban | Disadvantages of taking apixaban |
|---|---|
| No common food/drink interactions | No reversal agent – However, the half-life of the drug, which is the time it takes for the amount of drug in your blood stream to reduce by half, is much shorter. Furthermore, the risk of major bleeding is much lower with apixaban compared to warfarin. In addition a reversal agent is also currently in development. |
| There is no frequent monitoring as with having an INR test | |
| Fewer drug-drug interactions | |
| Lower risk of major bleeding | Patients with renal disease may need more frequent blood testing. |
| No frequent dose changes | |
| The drug works quickly once taken and has a large therapeutic window | |
| You will have 6 or 12 monthly reviews to check liver function, full blood count and kidney function | |

**Apixaban – key facts**

- Taken twice daily at either a 5mg or 2.5mg dose depending on renal function, weight and age.
- Can be put into a dossette box. If a dose is missed, the patient should take their dose immediately and then continue with twice daily intake as before.
- **For breastfeeding patients -** It is unknown whether apixaban is excreted in human milk.



More detailed information can be found in the patient information leaflet.

**The Switching Plan**

Your GP will issue a prescription for apixaban. The following plan should only be started after confirmation from the anticoagulation team. Until then you should cont. to take your warfarin as per normal and you should **not** start apixaban until told to do so.

| | |
|---|---|
| **Day 1** | **Last dose** of warfarin |
| **Day 2** | **Stop** warfarin |
| **Day 3** | - |
| **Day 4** | INR check<br>• If INR is **less than 2.0** you can start apixaban.<br><br>If INR is too high to start new treatment, book an INR test for 2 days' time. |

If you need any help or clarification with your switching plan please do not hesitate to contact us.

Anticoagulation Team
Royal United Hospital

**Email**: ruh-tr.AnticoagulationTeam@nhs.net

**Tel**: 01225825307
**Tel**: 01225821442

# Project recruitment

Sept 2017 - 8 GP practices initially approached – currently provide INR monitoring service.

Participation agreed with 6 GP practices

Barriers to recruitment :

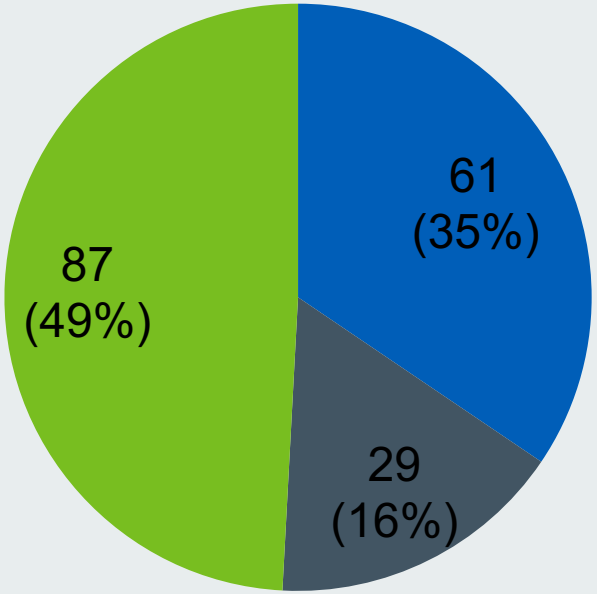
- Information governance
- Space allocation
- Practices merging

# 1. Optimise anticoagulation in patients currently taking warfarin

- Practice 1 (61/61 patients reviewed)
- Practice 2 (78/78 patients reviewed)
- Practice 3 (38/51 patients reviewed)


- Total no. patients reviewed so far = **177**
- Work ongoing with 3 GP surgeries (approx. n = 300)

# Reviews

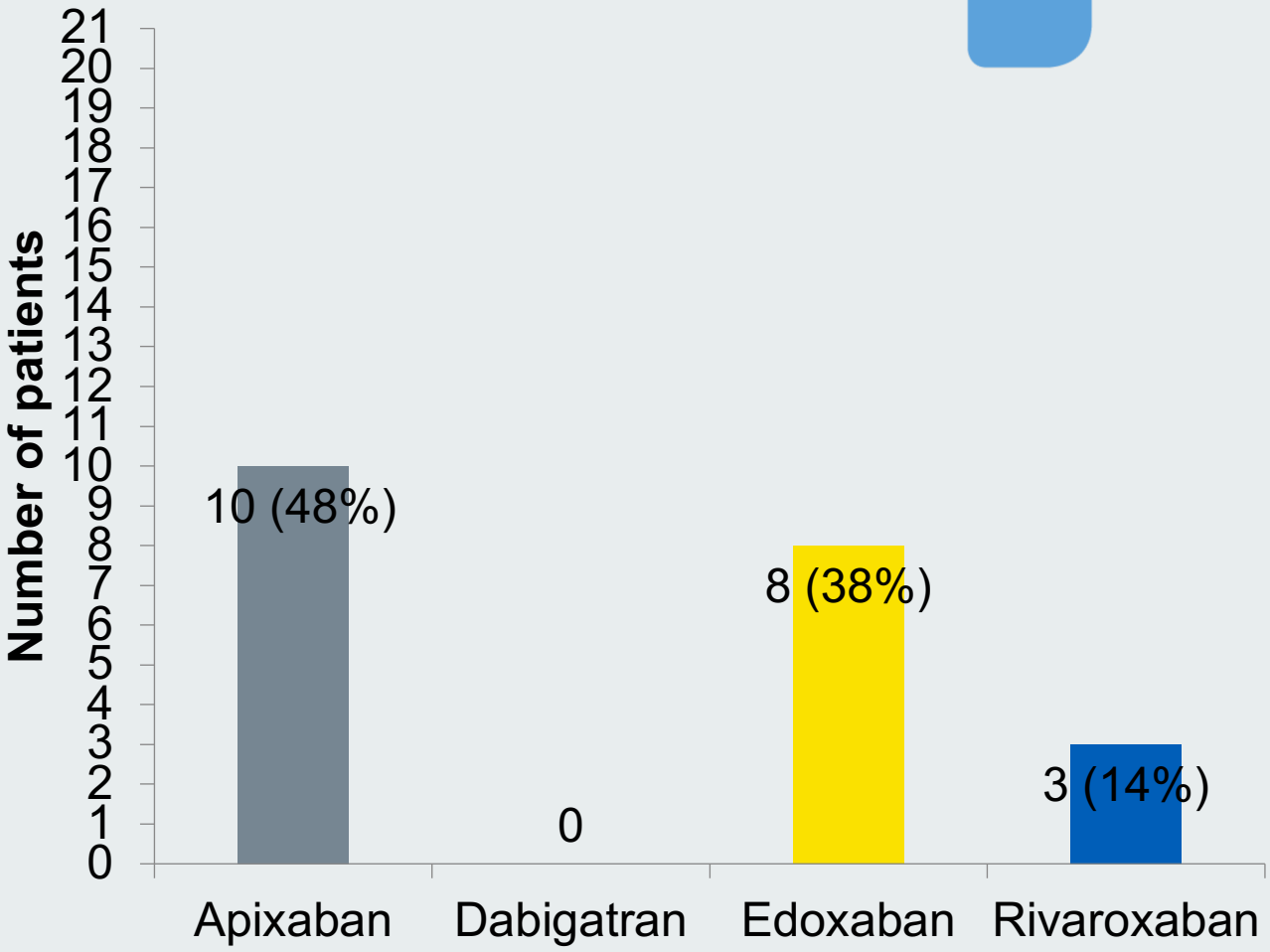



n = 177

- 20 minute review either face to face at the GP practice or over the telephone.
- If unable to contact a patient then a review was carried out without them and a recommendation made to the GP for follow up if needed.
- Reviews were carried out by either an anticoagulation nurse specialist or pharmacist.

# No. patients switched to DOAC

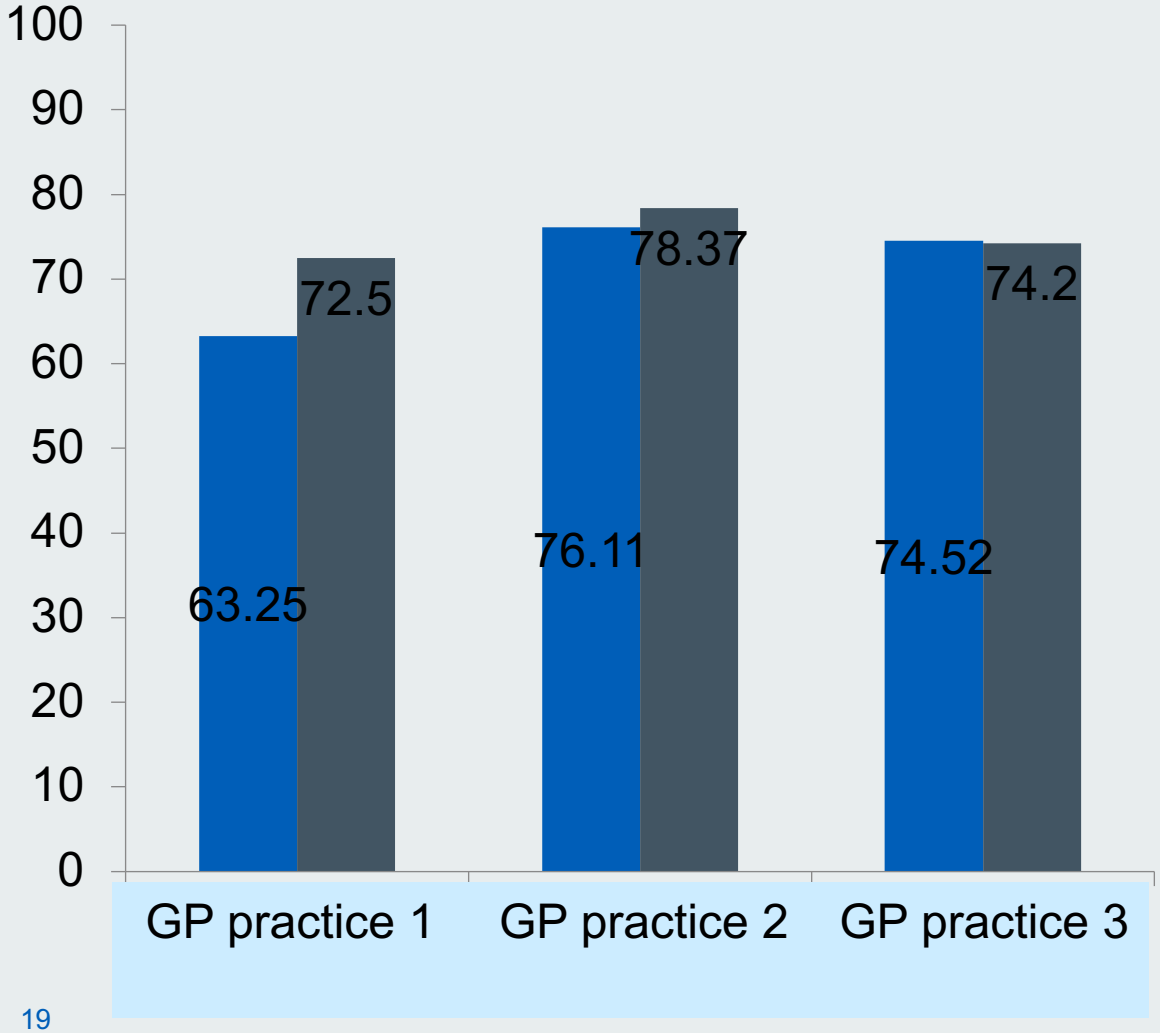
- n = 21 (out of 177 (12%))
- For patients reviewed without the patient present then 11 patients were referred to GP; to consider switching to a DOAC



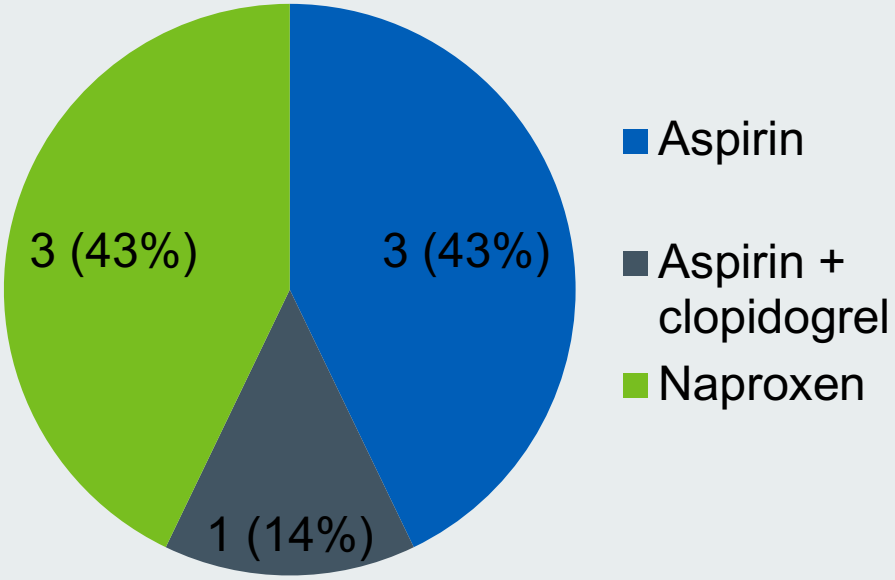
# Reasons for not switching

- Time in therapeutic range (TTR) > 75% (unless patient preference for DOAC)
- Unlicensed indication for DOAC
- On warfarin with a higher INR range (e.g. 2.5 - 3.5)
- Patient preference
- Renal impairment
- GI bleeding risk
- Interacting medication

# Average TTR for GP practice before and after reviews



# No. patients on concomitant NSAIDs or antiplatelets




n = 7 (= 4% out of 177 patients on warfarin who were reviewed)

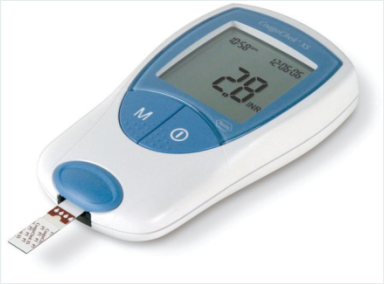
- For patients on concomitant NSAIDs or antiplatelet the GP was notified and a recommendation made.
- For patients on naproxen alternative analgesia was considered or a proton pump inhibitor added.
- If on aspirin for primary prevention, recommendation was to stop. If for secondary prevention and event was > 12 months ago then recommendation was stop or discuss with cardiology.

# Indication and duration of treatment

- All patients reviewed had an appropriate duration of treatment documented.
- 2 patients were on anticoagulation without a clear indication. These were referred to the thrombosis clinic for review.

# INR self-monitoring

- INR self monitoring was discussed as part of the review process where appropriate.
- This is not currently routinely available in the area.



# 2. Optimise anticoagulation in patients currently taking a DOAC

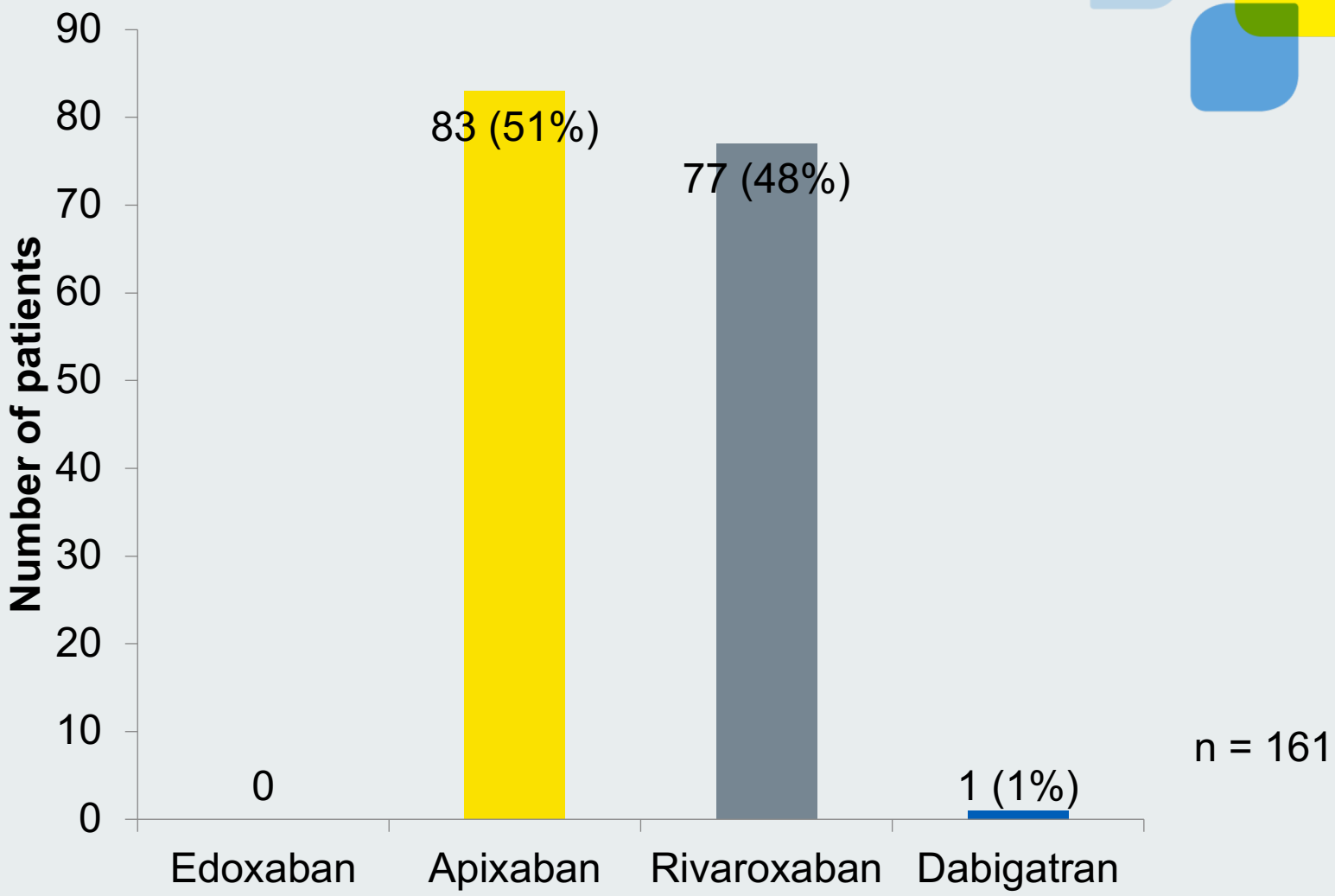
**Part 1**: Review by Anticoagulation Nurse at GP practice without patient, using patients records to check choice of DOAC, dose, renal function, weight, concomitant medication etc.

**Part 2**: Telephone call to patient by Anticoagulation Nurse or Anticoagulation Team member to check adherence, understanding, if taking with food (rivaroxaban), OTC/herbal medicines, side effects etc.

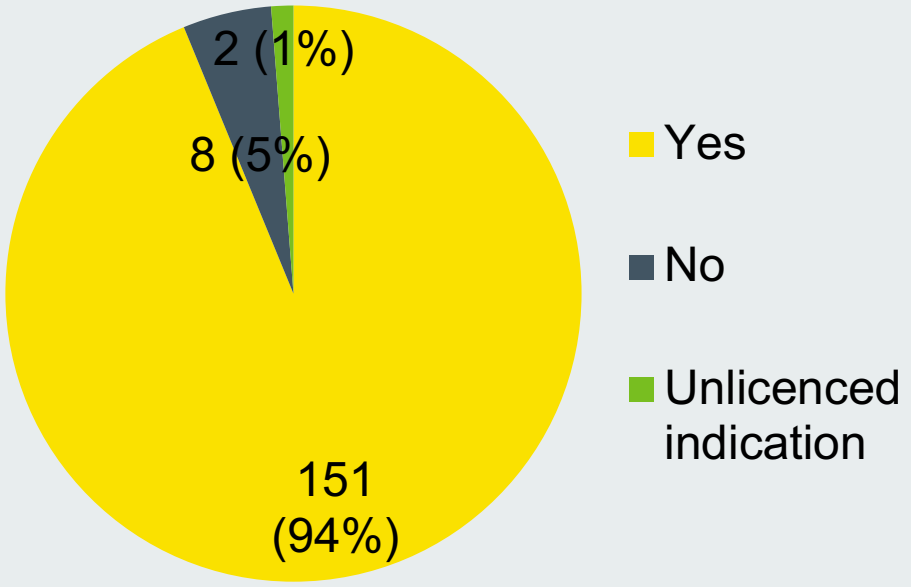

- Currently completed Part 1 for 161 patients at GP Practice 1.
- Part 2 currently underway for GP Practice 2.



# Choice of DOAC



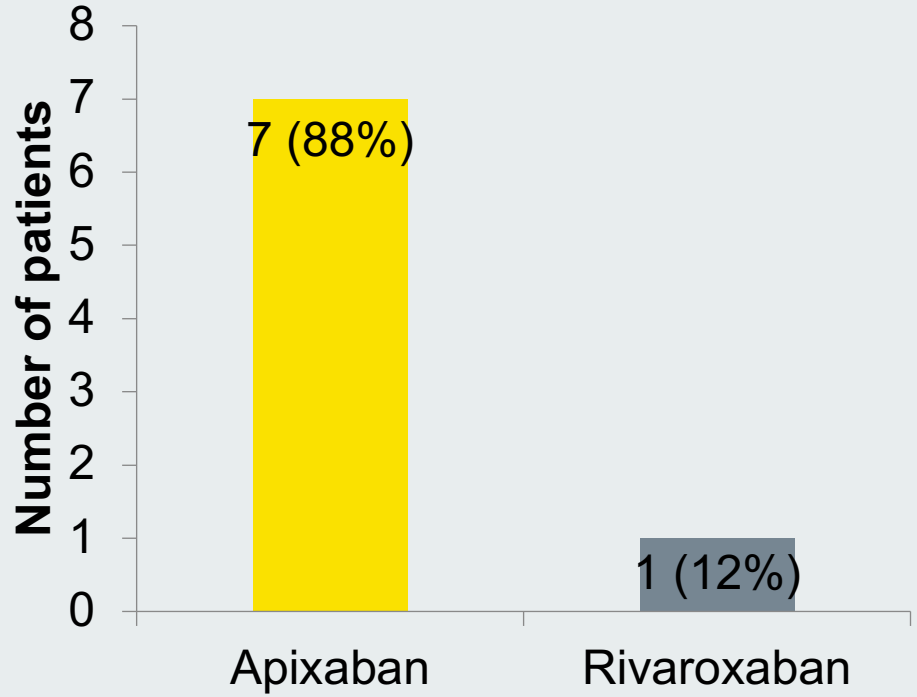
# No. patients on the correct dose of DOAC




n = 161

- Correct dose defined as per summary of product characteristics (SPC) for each DOAC.
- 2 patients on an unlicensed indication for DOAC – documented in medical record.
- GP notified in each case to review dose.
- 5 patients were deemed on to be on the correct dose, but had a weight of > 120kg. To check anti-Xa levels.

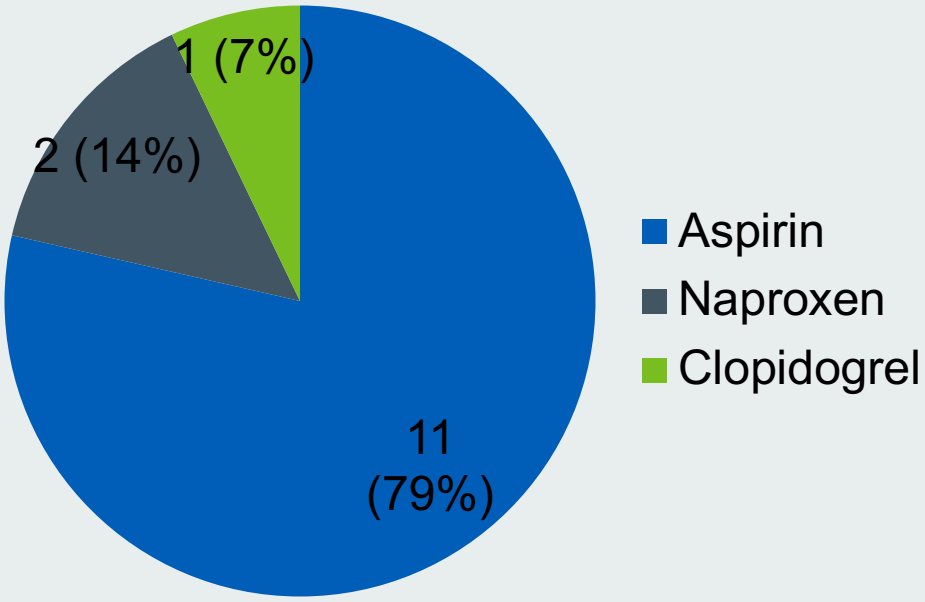
# Patients on the incorrect dose of DOAC




n = 8

- 6 out of 7 patients incorrectly prescribed apixaban were on the lower dose of 2.5mg BD when they should have been on the higher dose of 5mg BD.
- 1 patient was on the lower dose of rivaroxaban (15mg OD) and should have been on the higher dose of 20mg OD.

# No. patients on concomitant NSAIDs or antiplatelets




n = 14 (= 9% of patients prescribed a DOAC)

- Where patients were found to be on concomitant NSAIDs or antiplatelet medication the GP was notified and a recommendation made.
- For patients on naproxen then alternative analgesia was considered or addition of a proton pump inhibitor (PPI).
- For patients on aspirin then if on for primary prevention, recommendation was to stop. If on for secondary prevention and event was > 12 months ago then recommendation was stop or discuss with cardiology.

# 3. Review at risk patients who are not currently anticoagulated

- Currently part of the CCG prescribing incentive scheme with primary care
- GRASP-AF tool run every 6 months
- Identifies patients documented on GP system as having AF
- Patients who aren't anticoagulated are then reviewed by practice pharmacist and recommendations made to GP.
- Aim is for anticoagulation team at the RUH to provide support to the practice pharmacists and GPs when reviewing particularly difficult patients.

- AF screening tool funded by NHS England.

# 4. Knowledge and competency

- Support provided for GPs/ pharmacists and nurse practitioners
- Designated team to answer anticoagulation related queries.
- GP toolkits written (currently still in draft)
- Updated in house knowledge and training
- GP training day (June ’18)
- Southwest Haemostasis Group (May ‘18)

# Conclusions so far…

- An annual anticoagulation review is beneficial in improving overall TTR.
- An annual anticoagulation review helps ensure patients are on the most appropriate choice of anticoagulant and includes patients in the decision making process.
- 5% of patients on DOACs were prescribed a sub therapeutic dose, putting them at an increased risk of thrombosis, highlighting the need for a annual anticoagulation review.
- 9% of patients prescribed a DOAC and 5% of patients prescribed warfarin were also prescribed an antiplatelet or putting the patient at an increased risk of bleeding. Decision making on stopping antiplatelets in primary care can be difficult and highlights the potential benefit from a review done by a specialist team.

# Next steps

- Continue with reviews and data collection
- Patient experience team - feedback from GPs and patients
- Present to CCG
- Future projects
- Self monitoring
- Inpatient warfarin management
- Standardised counselling for initiation
- Bridging

# RUH Anticoagulation Team

**Tel**: 01225 825307

**Email**: ruh-tr.AnticoagulationTeam@nhs.net

# Manging anticoagulation therapy for stroke prevention - who cares wins

David Fitzmaurice
Professor of Primary Care Research
University of Warwick

# Stroke prevention and atrial fibrillation

- Epidemiology of atrial fibrillation
  - How common is it?
  - What is it's impact?
- Stroke prevention in atrial fibrillation
  - Anticoagulation versus antiplatelet therapy
  - Rate versus rhythm control
- INR control
  - Target INR
  - Impact of quality of INR control
- New Agents

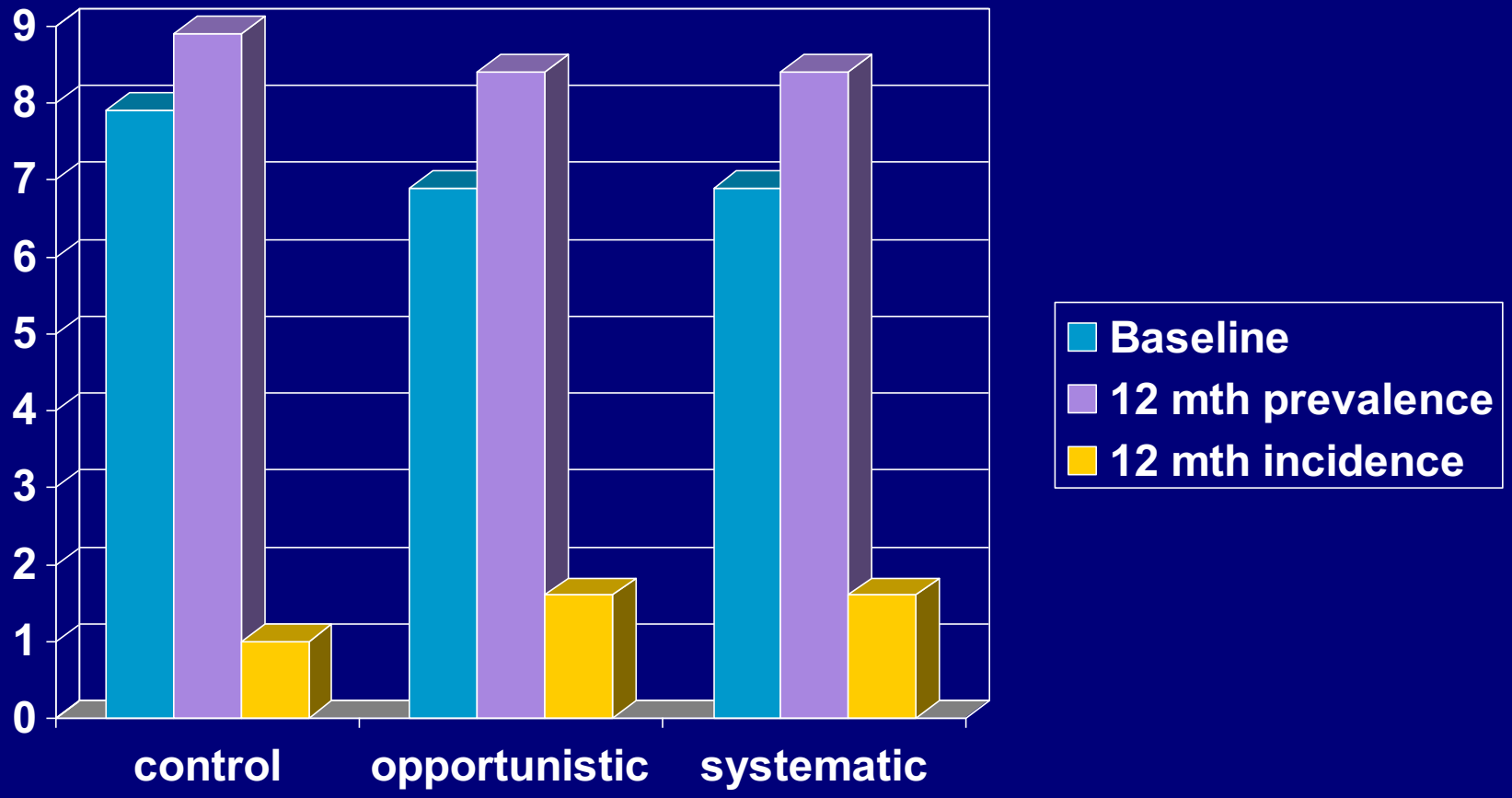
BMJ

RESEARCH

# Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial

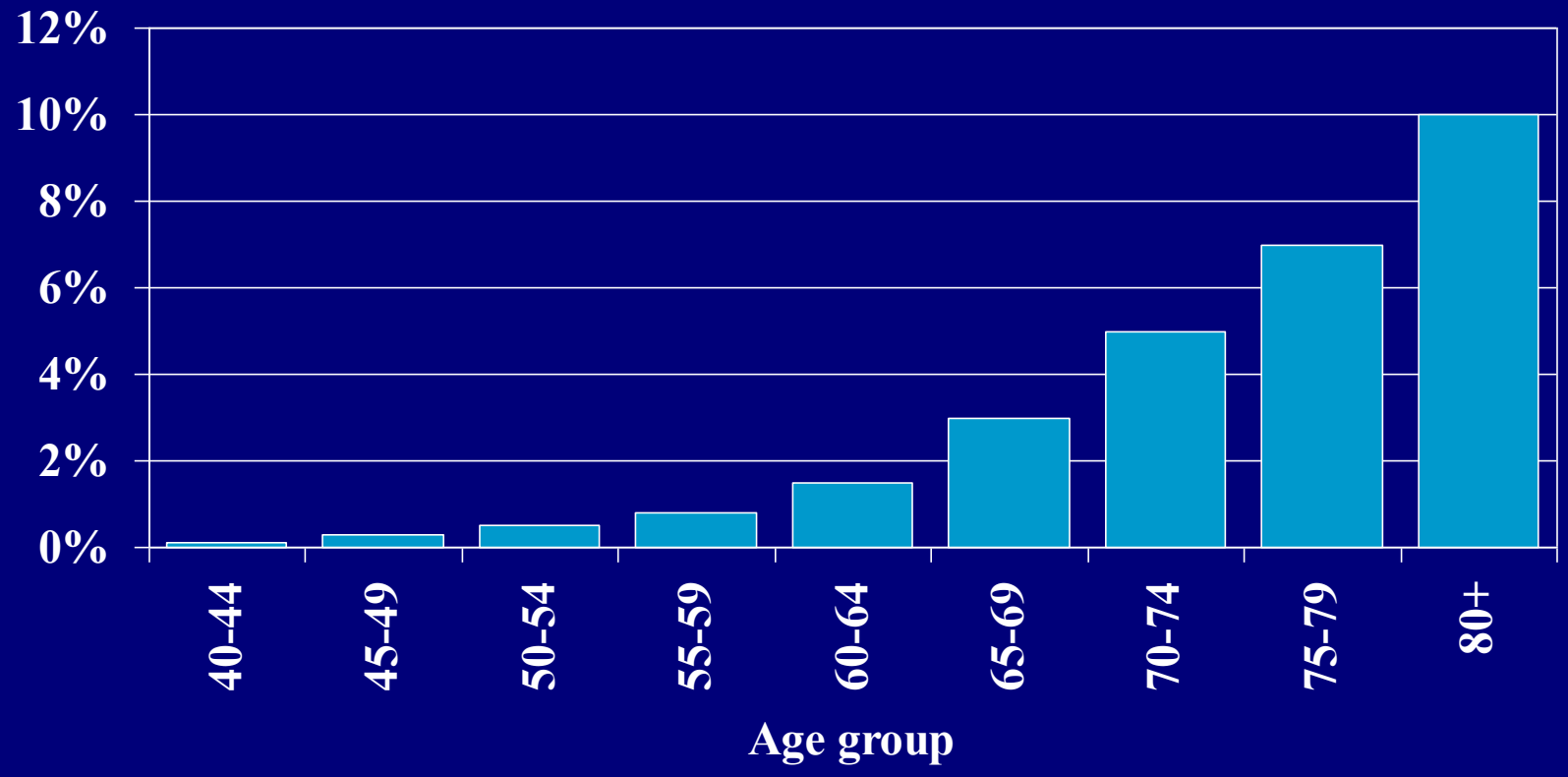
David A Fitzmaurice, professor of primary care,[1] F D Richard Hobbs, professor, head of department,[1] Sue Jowett, research fellow,[1] Jonathon Mant, reader,[1] Ellen T Murray, research fellow,[1] Roger Holder, head of statistics,[1] J P Raftery, professor of health technology assessment,[2] S Bryan, professor of health economics,[3] Michael Davies, consultant cardiologist,[4] Gregory Y H Lip, professor of cardiovascular medicine,[5] T F Allan, senior lecturer[6]

# Prevalence & detection rates of new cases of AF in people aged >65




SAFE study, BMJ 2007

# Age specific prevalence of AF

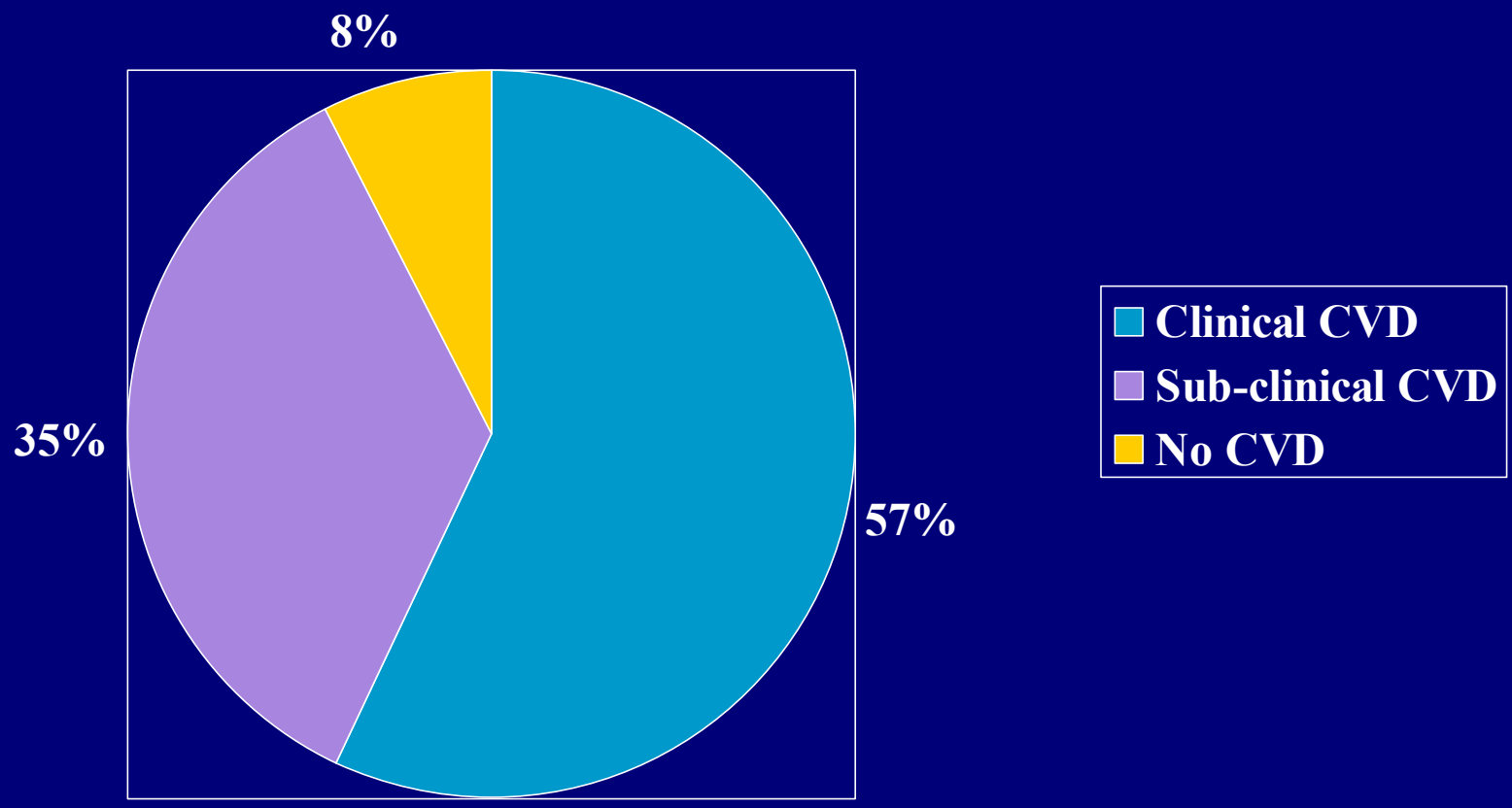


# Descriptive epidemiology of AF

- Becoming more common
  - Framingham: 3 fold increase 1968 – 1989
- 25% paroxysmal
- More common in men than women
- Many have underlying cardiac disease

# Prevalence of cardiovascular disease in AF

*Furberg et al 1994*



# Impact of AF

- Increased risk of death
- Increased risk of stroke
- Associated with higher mortality from CHD and heart failure
- ?Impaired cognition/ dementia

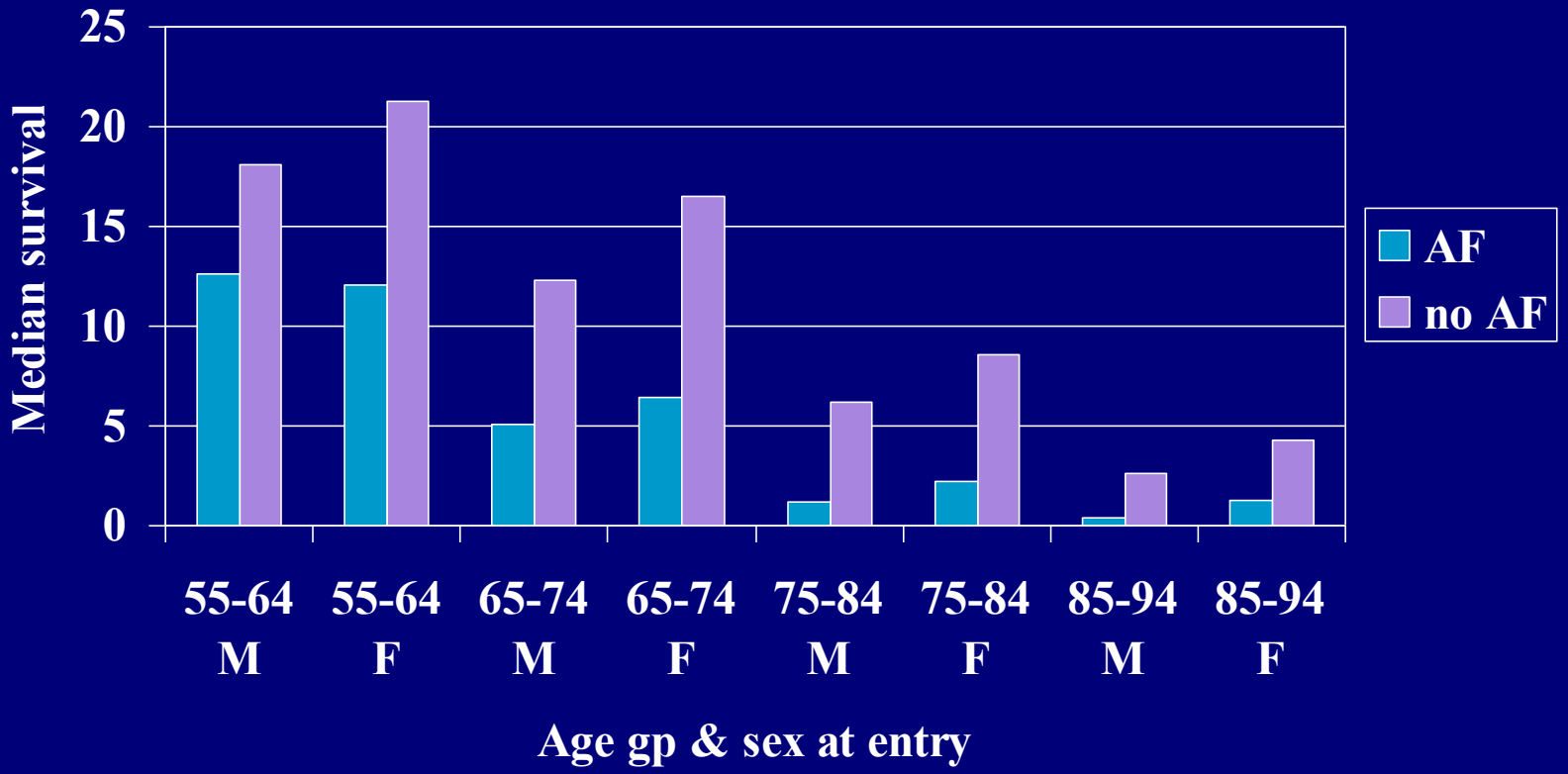
# AF and mortality – the Framingham study

*Circulation 1998*

- 5209 residents aged 28-62 enrolled in 1948
- 621 new cases of AF identified over 40 years of follow up

# AF and mortality – the Framingham study

*Circulation 1998*



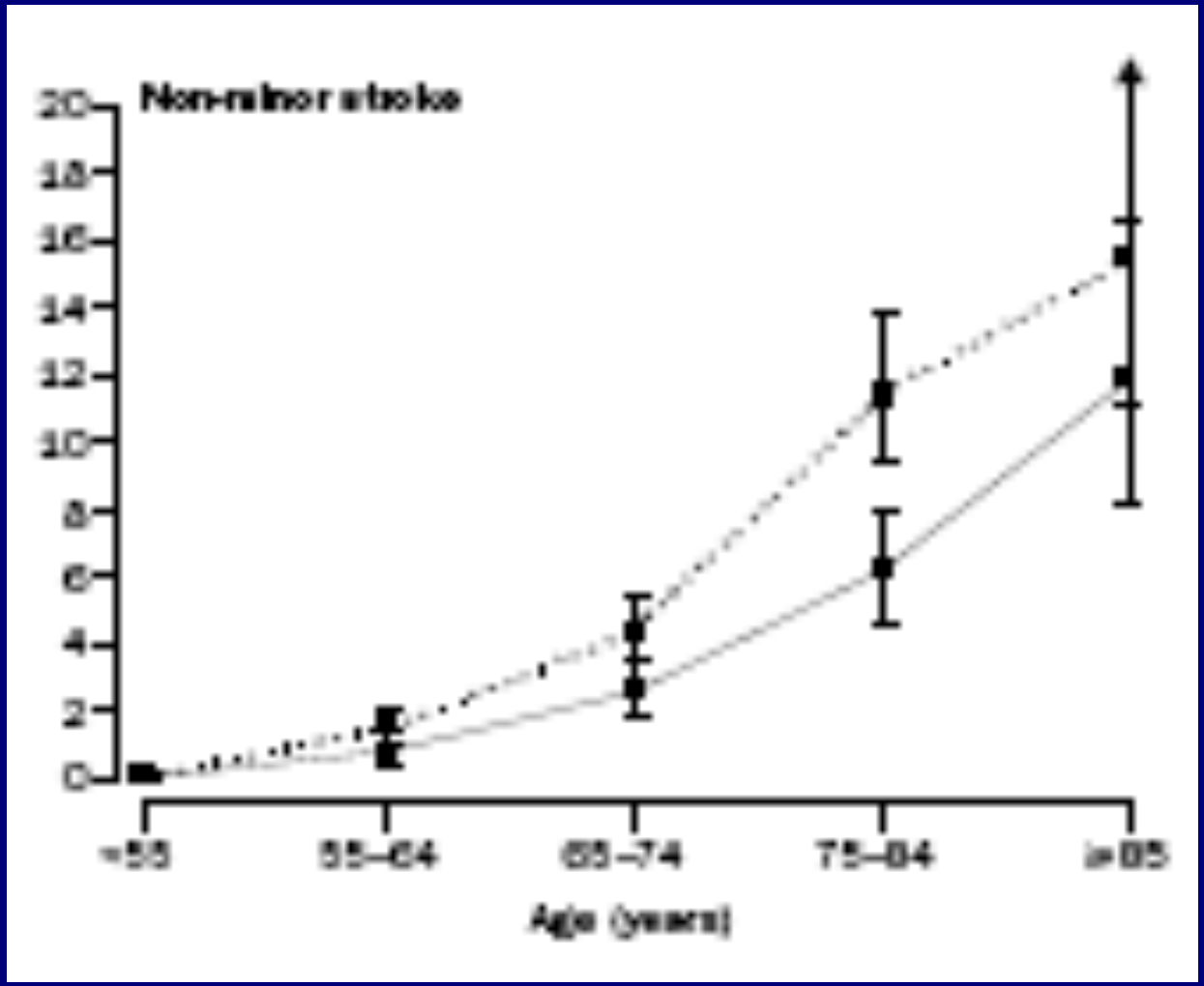
# Odds ratios for death

- Multi-variate analysis:
  - Men: 1.5 (95% CI: 1.2 – 1.8)
  - Women: 1.9 (95% CI 1.5 – 2.2)
- CHD commonest cause of death

# AF and stroke

- Five fold increase in risk of stroke
- What does this mean for an individual patient?
  - Need to know risk of stroke
  - Factors that increase risk of stroke

# Change in stroke incidence 1981-2004




*Rothwell et al, Lancet 2004; 363:1925-33*

# $CHADS_2$ $CHA_2DS_2VASc$

## CHADS2 risk Score

| Score | |
|---|---|
| CHF | 1 |
| Hypertension | 1 |
| Age >75 | 1 |
| Diabetes | 1 |
| Stroke or TIA | 2 |

## CHA2DS2-VASc risk

| | |
|---|---|
| CHF or LVEF $\leq$ 40% | 1 |
| Hypertension | 1 |
| Age $\geq$ 75 | 2 |
| Diabetes | 1 |
| Stroke / TIA | 2 |
| Thromboembolism | |
| Vascular Disease | 1 |
| Age 65-74 | 1 |
| Female | 1 |

# HAS-BLED Score for bleeding risk on oral anticoagulation in AF

| Feature | Score if present |
|---|---|
| Hypertension (systolic $\geq$ 160mmHg | 1 |
| Abnormal renal function | 1 |
| Abnormal liver function | 1 |
| Age $\geq$ 65 years | 1 |
| Stroke in past | 1 |
| Bleeding | 1 |
| Labile INRs | 1 |
| Taking other drugs as well | 1 |
| Alcohol intake at same time | 1 |

Increased 1-year bleed risk with score of 3 or more on anticoagulant.
Is this sufficient to justify caution or more regular review?

# Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation – an individual patient meta-analysis

Walraven et al JAMA Nov 2002

# Walraven et al

- 7 trials
- 4052 patients in AF
- Randomised to full anticoagulation or aspirin

# Comparison of effect on outcome of oral anticoagulants and aspirin

| Outcome | Hazard ratio | P value |
|---|---|---|
| Stroke (all) | 0.55 (0.43-0.71) | < 0.001 |
| Cardiovascular events | 0.71 (0.59-0.85) | < 0.001 |
| Vascular death | 0.95 (0.75-1.20) | 0.18 |
| Major bleeding | 1.71 (1.21-2.41) | 0.02 |
| Death | 0.93 (0.76-1.13) | 0.32 |

Hazard ratio < 1 favours anticoagulation

# Warfarin versus aspirin: effect of age – 1. Under 75s (Walraven et al)

| Outcome | On aspirin | On warfarin | Rel Risk Reduction / increase | NNT /H pa |
|---|---|---|---|---|
| Ischaemic stroke | 3.4% | 1.3% | 62% | 48 |
| Major bleed | 1.2% | 1.8% | 150% | 167 |

# Warfarin versus aspirin: effect of age – 2. Over 75s (Walraven et al)

| Outcome | On aspirin | On warfarin | Rel Risk Reduction / increase | NNT /H pa |
|---|---|---|---|---|
| Ischaemic stroke | 5.9% | 3.7% | 47% | 46 |
| Major bleed | 1.5% | 3.2% | 213% | 59 |

# BAFTA: RCT of warfarin vs aspirin for stroke prevention in AF in a primary care population aged over 75 *Mant et al Lancet 2007;370:493-503*

- Aim:
- To compare the incidence of fatal and non-fatal disabling stroke (ischaemic and haemorrhagic), intra-cranial haemorrhage and other significant arterial embolism in patients randomised to warfarin (target INR 2-3) or aspirin (75mg)

# Results: primary end point

- Risk of primary end point:
- Warfarin v aspirin
- 1.8% p.a v 3.8% p.a
- RR 0.48 (0.28-0.80)
- NNT: 50 for 1 year
- p = 0.0027

Nature of Primary end points

| | warfarin | aspirin |
|---|---|---|
| Stroke | **21** | **44** |
| *-ischaemic* | *10* | *32* |
| *-haem* | *6* | *5* |
| Subdural | **2** | **1** |
| Embolism | **1** | **3** |
| Total | **24** | **48** |

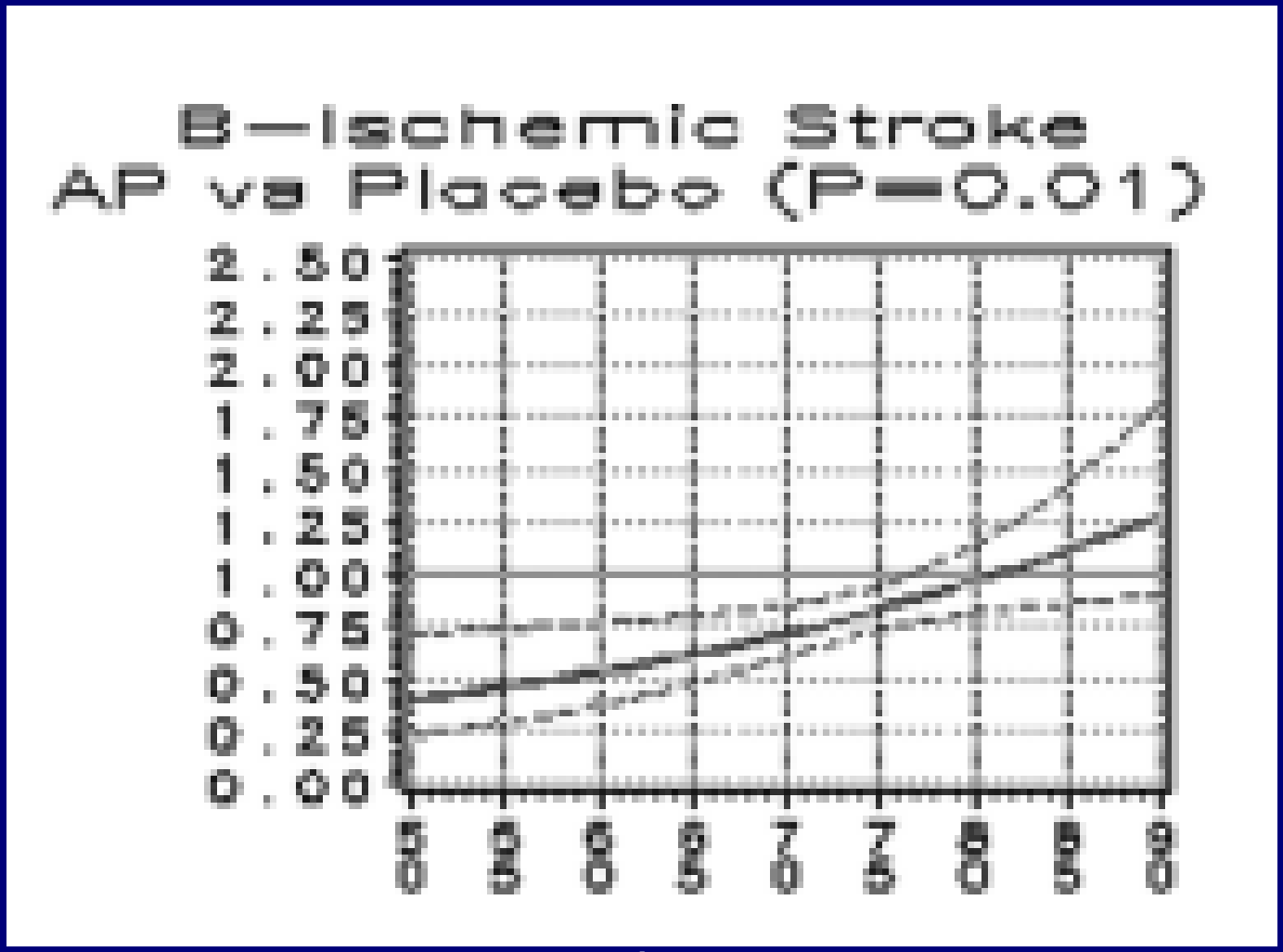
# Secondary outcomes: haemorrhage – risk per annum

| | warfarin | aspirin | RR (95% CI) |
|---|---|---|---|
| Major extra-cranial | 1.4% | 1.6% | 0.87 (0.43-1.73) |
| Other hospital admission | 1.8% | 1.5% | 1.22 (0.64-2.36) |
| All major (including stroke and sub-dural) | 1.9% | 2.0% | 0.96 (0.53-1.75) |

# Risk of major haemorrhage by age (% p.a)

| | Warfarin | Aspirin | RR | P value (interaction) |
|---|---|---|---|---|
| 75-79 | 1.1 | 0.8 | 1.44 | 0.53 |
| 80-84 | 2.3 | 2.4 | 0.96 | 0.80 |
| 85+ | 2.9 | 3.7 | 0.77 | |

# Influence of age on effect of aspirin in stroke prevention in AF




Van Walraven et al, Stroke 2009

# Summary of BAFTA

- Anticoagulation significantly more effective than aspirin in preventing stroke
  - Benefit of warfarin likely to be underestimated due to treatment cross overs and patient selection
- No difference in prevention of other vascular events
- No difference in risk of major haemorrhage

# Rate versus rhythm control

- The AFFIRM trial (NEJM Dec 2002)
  - 4,060 patients in AF age 65 or over or other risk factors for stroke/death
  - Patients randomised to:
    - Rhythm control: cardioversion as necessary; +/- drugs: amiodarone; disopyramide; flecainide; dofetilide etc.
    - Rate control: beta-blockers; verapamil; diltiazem; digoxin.
  - Anticoagulation: could be stopped if sinus rhythm maintained

# RCT of rhythm versus rate control in atrial fibrillation: mortality after 5 years of follow up in 4,000 patients


| No. of Deaths | | number (percent) | | | | |
|---|---|---|---|---|---|---|
| Rhythm control | 0 | 80 (4) | 176 (9) | 257 (13) | 314 (18) | 352 (24) |
| Rate control | 0 | 78 (4) | 148 (7) | 210 (11) | 276 (16) | 306 (21) |

# Results of AFFIRM

- After 5 yr follow up:
  - Death rate: 24% (rhythm control) versus 21% (rate control). P = 0.08.
  - Secondary end-points all favoured rate control:
    - Fewer hospitalisations
    - Fewer pulmonary events
    - Fewer GI events
    - Fewer serious arrythmias

## "on treatment" analysis of AFFIRM: what factors are associated with improved survival? *(Circulation 2004)*

- Improved survival
  - Warfarin use (0.5)
  - Sinus Rhythm (0.53)
- No association
  - Sex; hypertension; LA enlargement;
  - B blockers
  - Calcium channel blockers
- Worse survival
  - Older age (1.05 per yr)
  - CAD; CHF; DM; stroke/TIA
  - Smoking
  - LV dysfunction
  - Mitral regurgitation
  - Digoxin use
  - Rhythm control drug use

## Alternatives to warfarin

- At least same anti-thrombotic effect
- Lower risk of bleeding – especially intracranial bleeding
- Few other side-effects
- Oral bioavailability – once or twice daily
- No food or drug interactions
- Broad therapeutic window at standard dosing
- Stable anticoagulation without frequent laboratory monitoring
- Good patient acceptability and long-term tolerance

# Pharmacology of novel anticoagulants

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| **Mechanism of action** | Selective direct FIIa inhibitor | Selective direct FXa inhibitor | Selective direct FXa inhibitor | Competitive inhibitor of FXa |
| **Bioavailability** | Oral prodrug with poor oral bioavailability | Good oral bioavailability | Good oral bioavailability | Good oral bioavailability |
| **$T_{½}$** | 12 - 17 hours (80% renal excretion) | 6 - 9 hours | 12 hours | 9 -11 hours |
| **Dosing** | Twice daily | Once daily | Twice daily | Once daily |
| **Time to max effect** | 1 - 4 h | 1 - 4 h | 1 - 4 h | 1 - 4 hr |

# New anticoagulants (1)

- Dabigatran RE-LY trial *NEJM 2009; 361:1139*
  - 150mg bd v warfarin
    - stroke: 1.0% vs 1.6%, RR 0.64 (0.51-0.81)
    - death: 3.6% v 4.1%, RR 0.88 (0.77-1.00)
    - major bleed: 3.3% v 3.6%, RR 0.93 (0.81-1.07)
  - 110mg bd v warfarin
    - stroke: 1.4% vs 1.6%, RR 0.92 (0.74-1.13)
    - death: 3.7% v 4.1%, RR 0.91 (0.80-1.03)
    - major bleed: 2.9% vs 3.6%, RR 0.80 (0.70-0.93)

# New anticoagulants (2)

- Rivaroxaban ROCKET-AF *NEJM 2011*
  - 20 mg od
  - stroke 2.1% vs 2.4%, RR 0.88 (0.75-1.03)
  - death 1.9% vs 2.2%, RR 0.85 (0.70-1.02) on treatment
  - major bleeding 3.6% vs 3.4%, RR 1.04 (0.9-1.2) on treatment

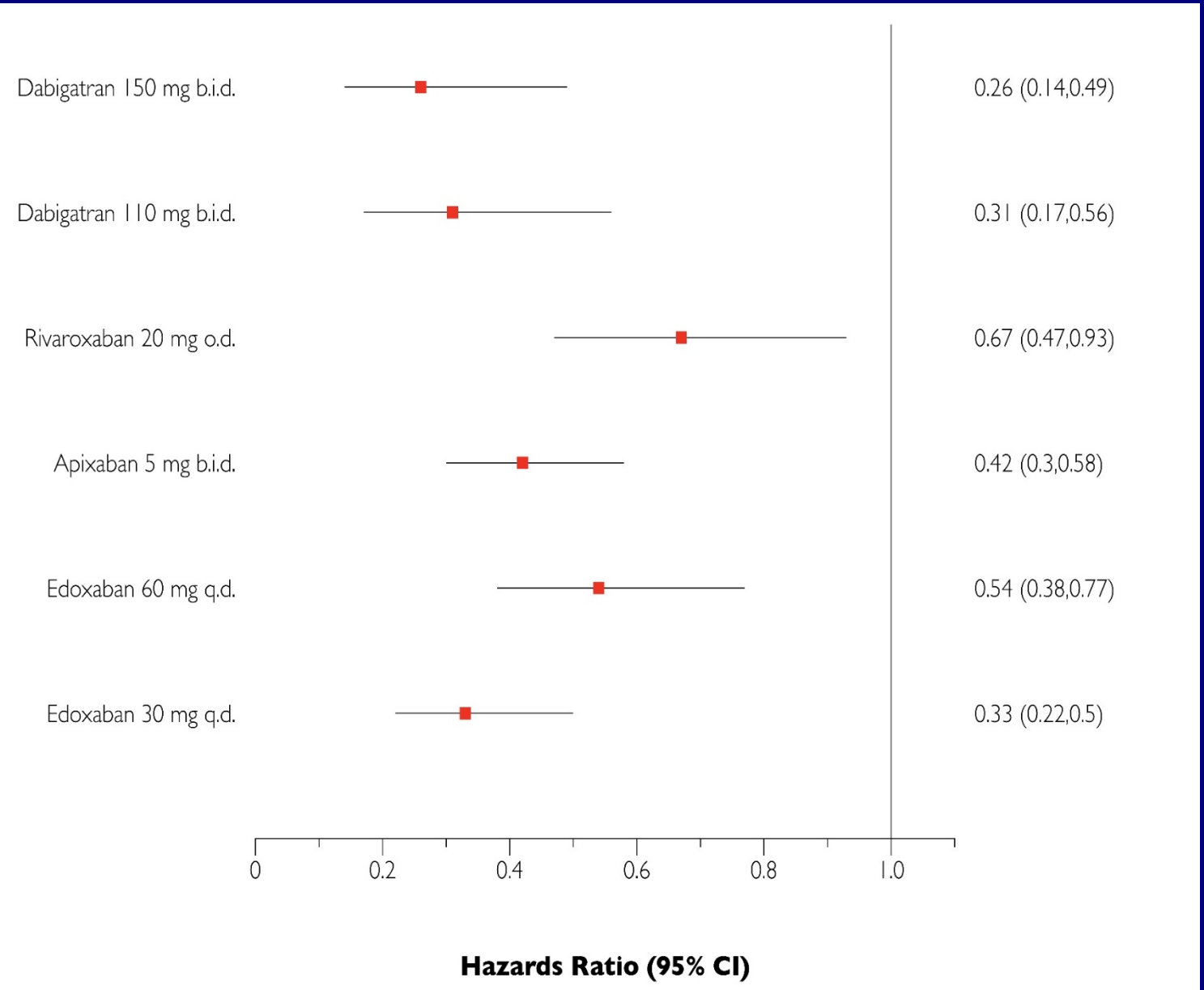
# New anticoagulants (3)

- Apixaban: ARISTOTLE *NEJM 2011*
  - 5mg bd
  - stroke 1.3% vs 1.6%, RR 0.79 (0.66-0.95)
  - death 3.5% vs 3.9%,  RR 0.89 (0.80-0.99)
  - major bleeding 2.1% vs 3.1%, RR 0.69 (0.6-0.8) on treatment

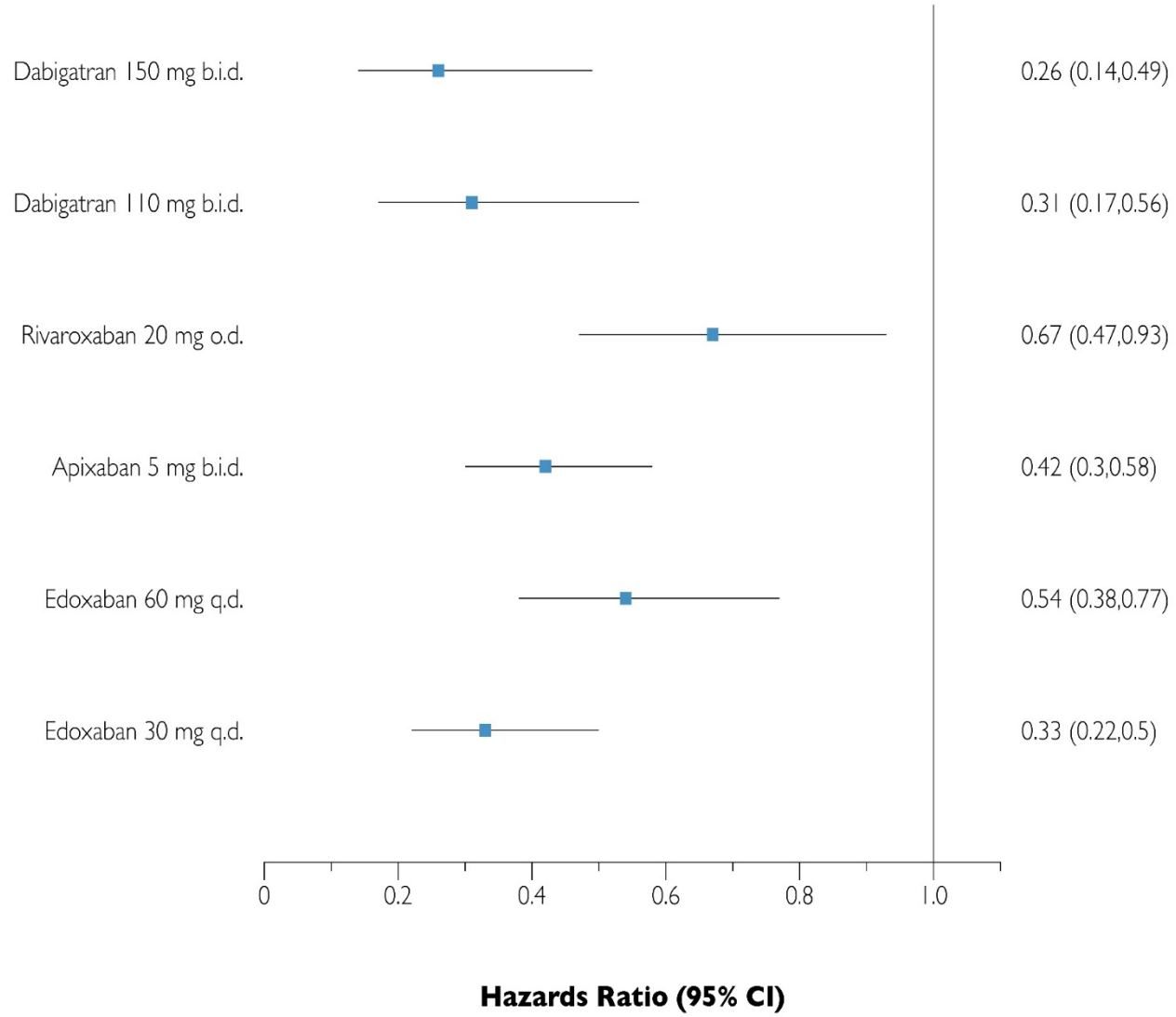
# New Anticoagulants (4)

- Edoxaban – Engage AF TIMI-48 *NEJM 2013*
  - 60mg od v warfarin
    - stroke 1.2% vs 1.5% RR 0.79 (0.63-0.99)
    - death 4.0% vs 4.4%  RR 0.92 (0.83-1.01)
    - major bleeding 2.8% vs 3.4% RR 0.80 (0.71-0.91)
  - 30mg od v warfarin
    - stroke 1.6% vs 1.5%  RR1.07 (0.87-1.31)
    - death 3.8% vs 4.4%  RR 0.87 (0.79-0.96)
    - major bleeding 1.6% vs 3.4%  RR 0.47 (0.41-0.55)

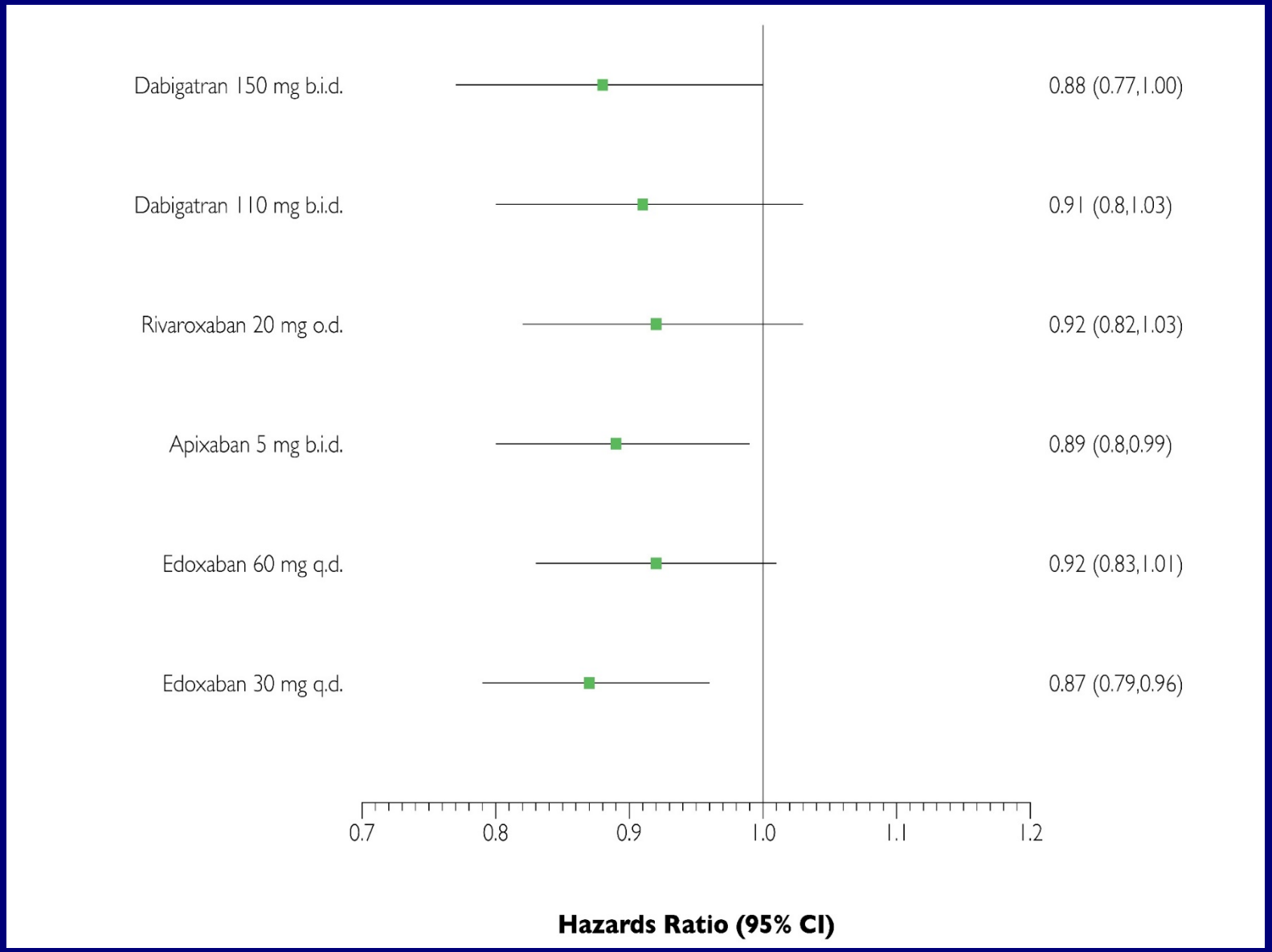
# New antithrombotic therapies compared to warfarin
## Stroke or systemic embolism



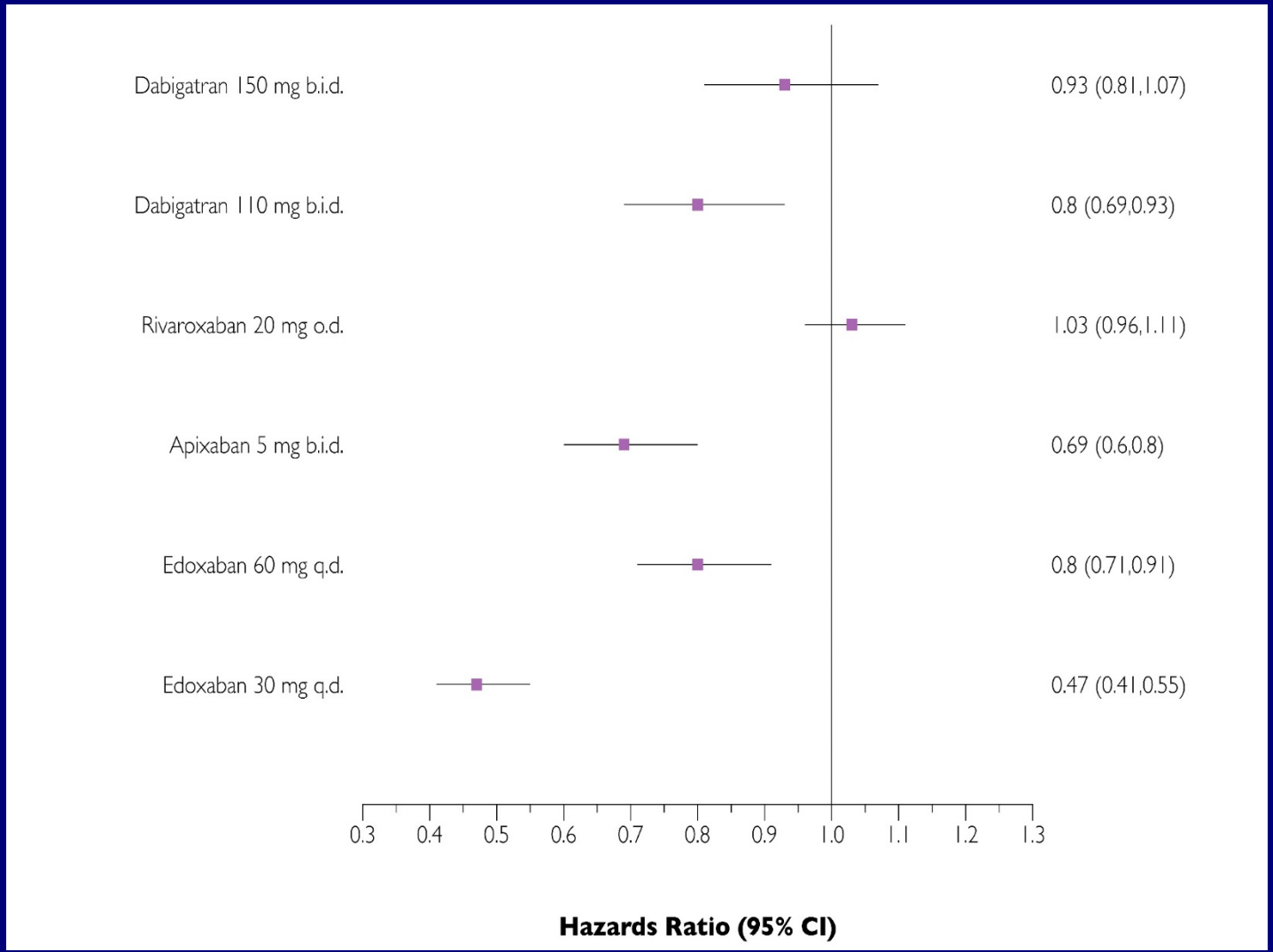
# New antithrombotic therapies compared to warfarin
# Haemorrhagic stroke



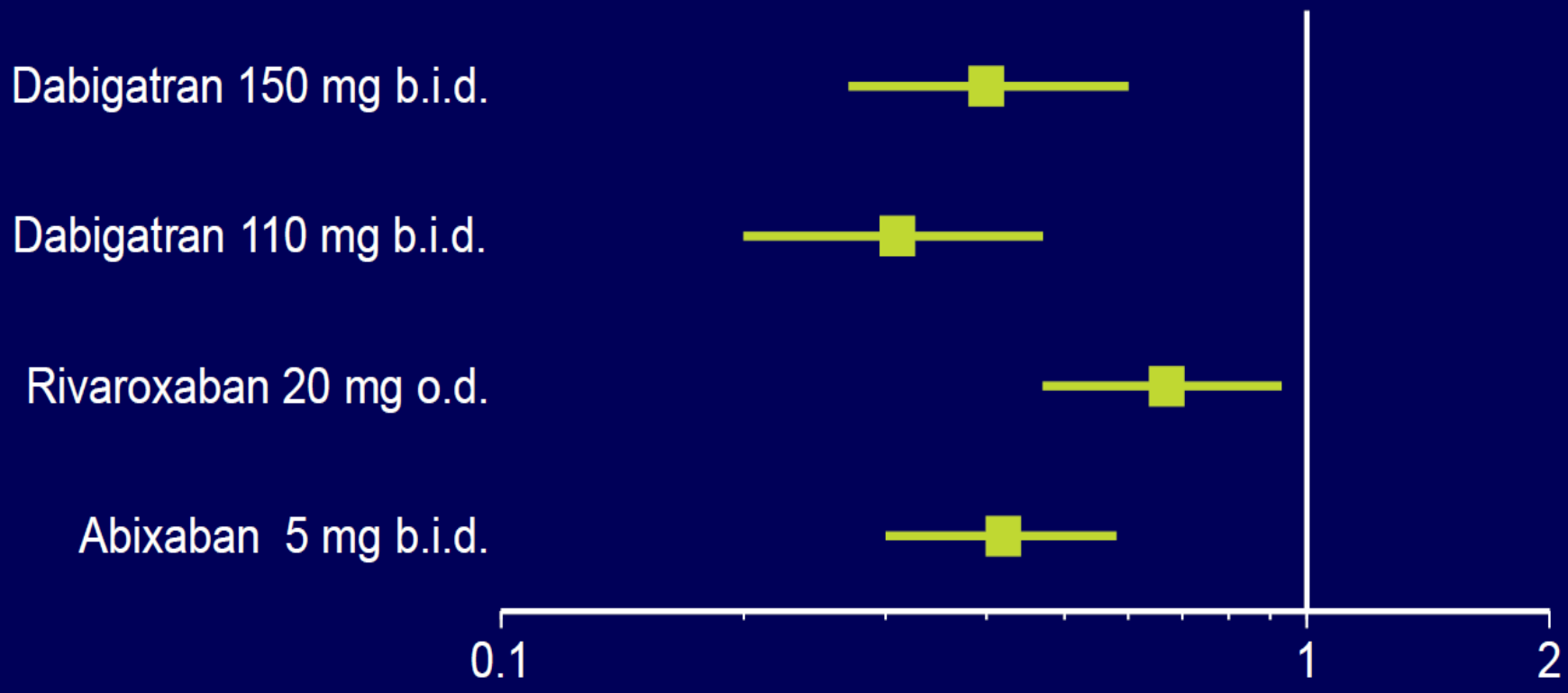
# New antithrombotic therapies compared to warfarin
# All-cause mortality



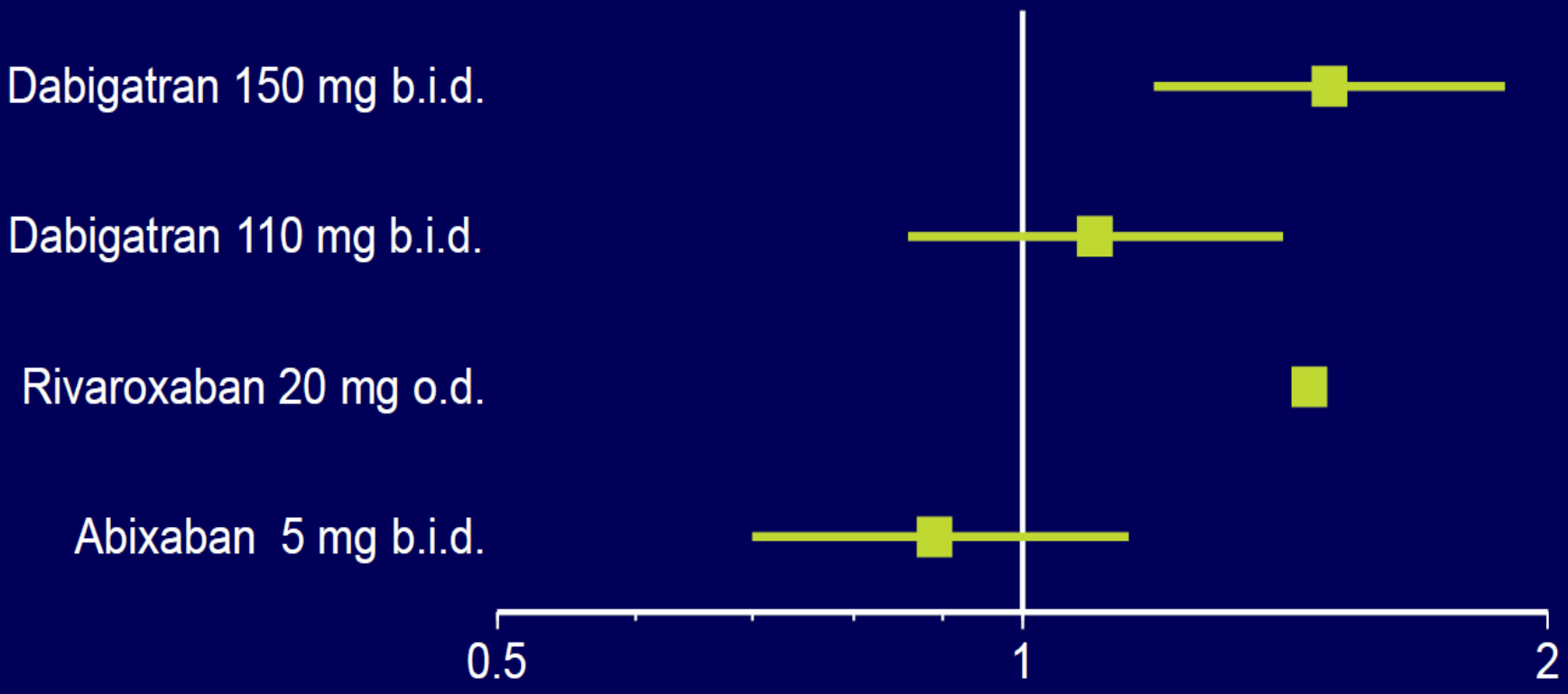
# New antithrombotic therapies compared to warfarin
# Major bleeding



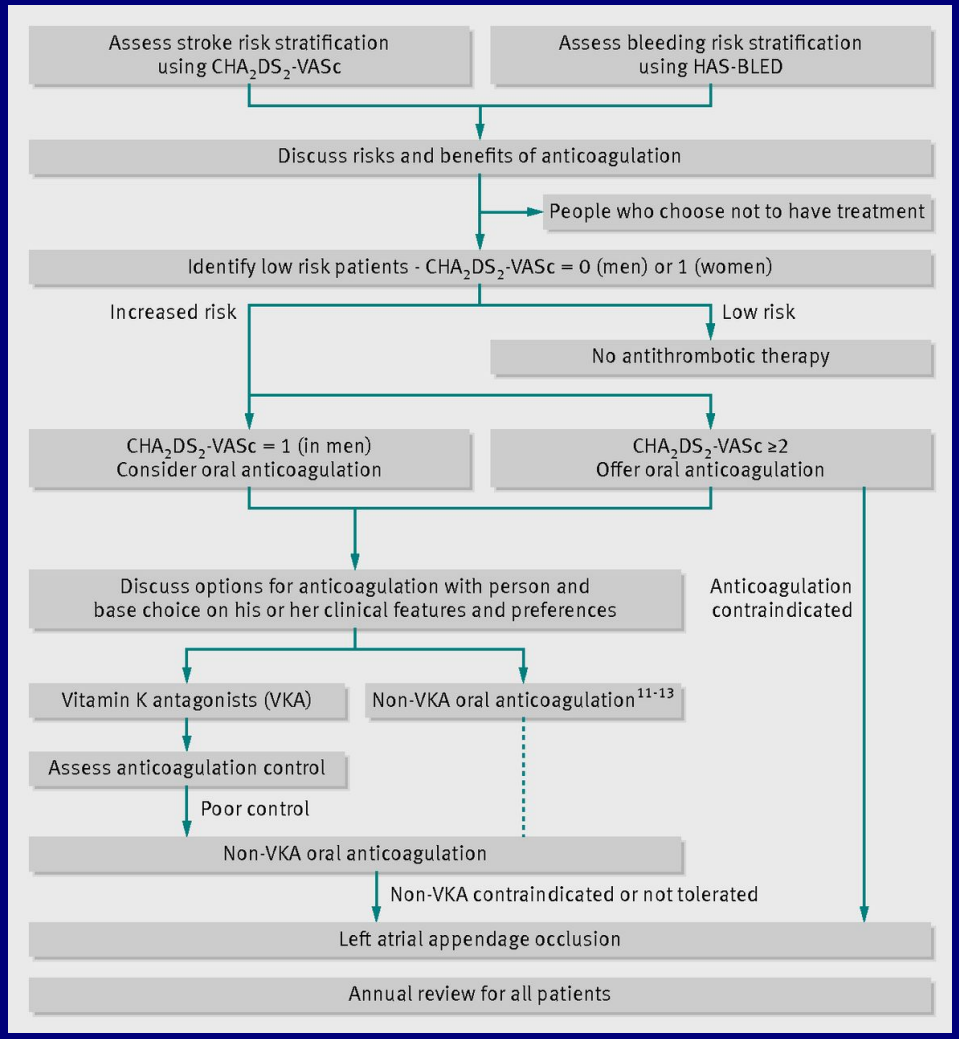
# New antithrombotic therapies compared to warfarin
# Intracranial hemorrhage



# New antithrombotic therapies compared to warfarin
# Gastrointestinal bleeding



# Stroke prevention in people with non-valvular atrial fibrillation.




Jones C et al. BMJ 2014;348:bmj.g3655

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# Conclusions

- Atrial fibrillation is associated with major morbidity
- Impact of AF will increase
  - Better survival of people with CHD
  - Ageing population
- Warfarin is highly effective at reducing risk of stroke
- Newer agents are here
- Aspirin has no role in stroke prevention in atrial fibrillation
- Rate control 1st line

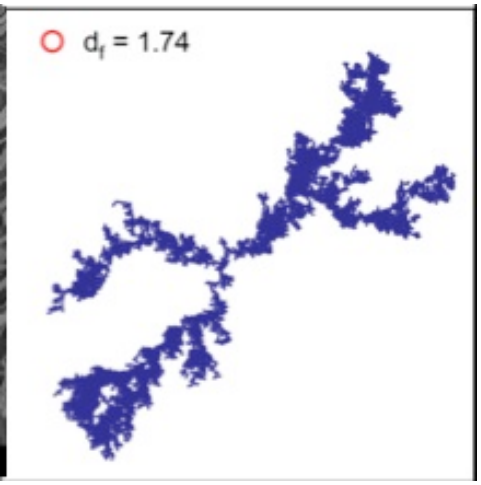
# Cancer Associated Thrombosis
# An update.

Simon Noble
Marie Curie Professor of Supportive and Palliative Medicine
Marie Curie Palliative Care Research Centre
Cardiff University

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Marie Curie
Care and support through terminal illness

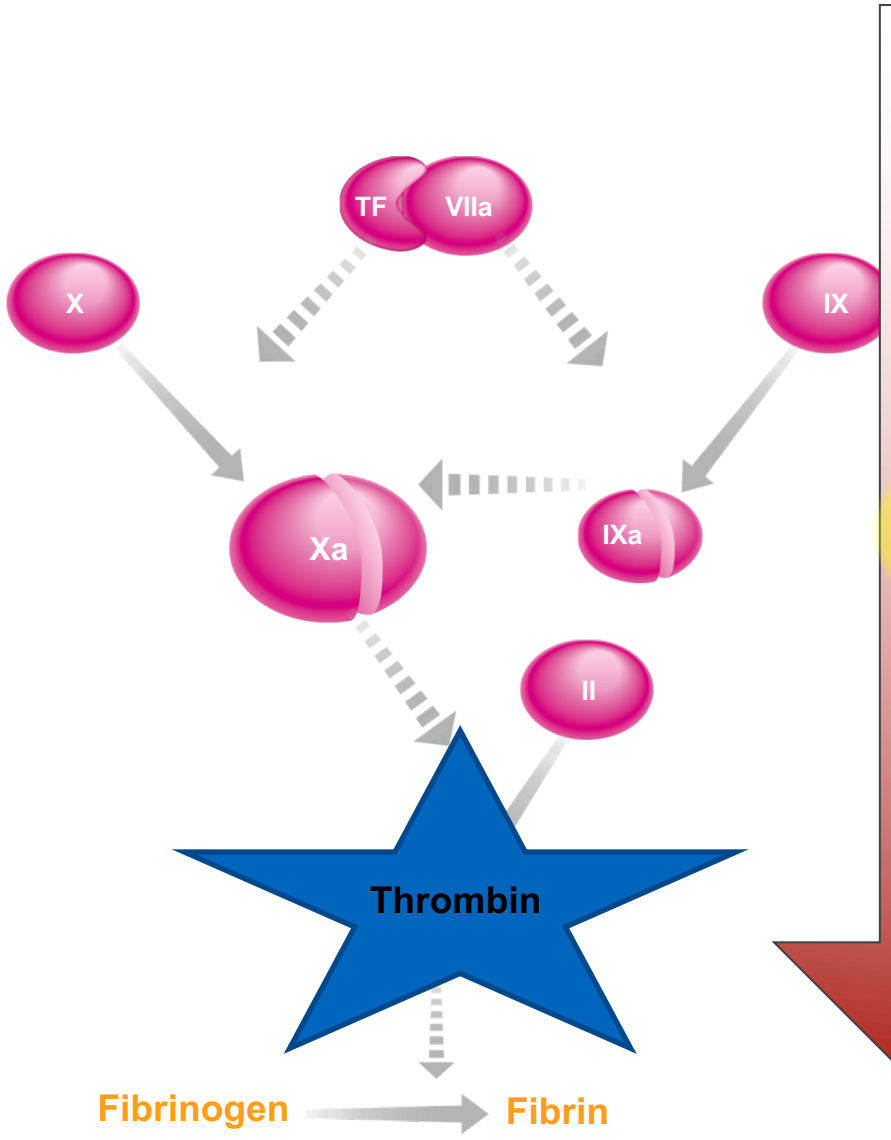
# The coagulation pathway

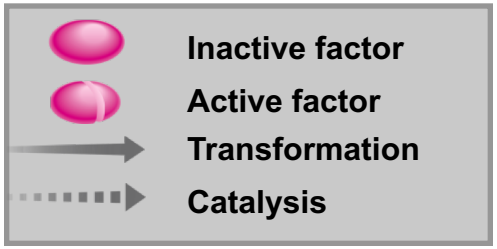


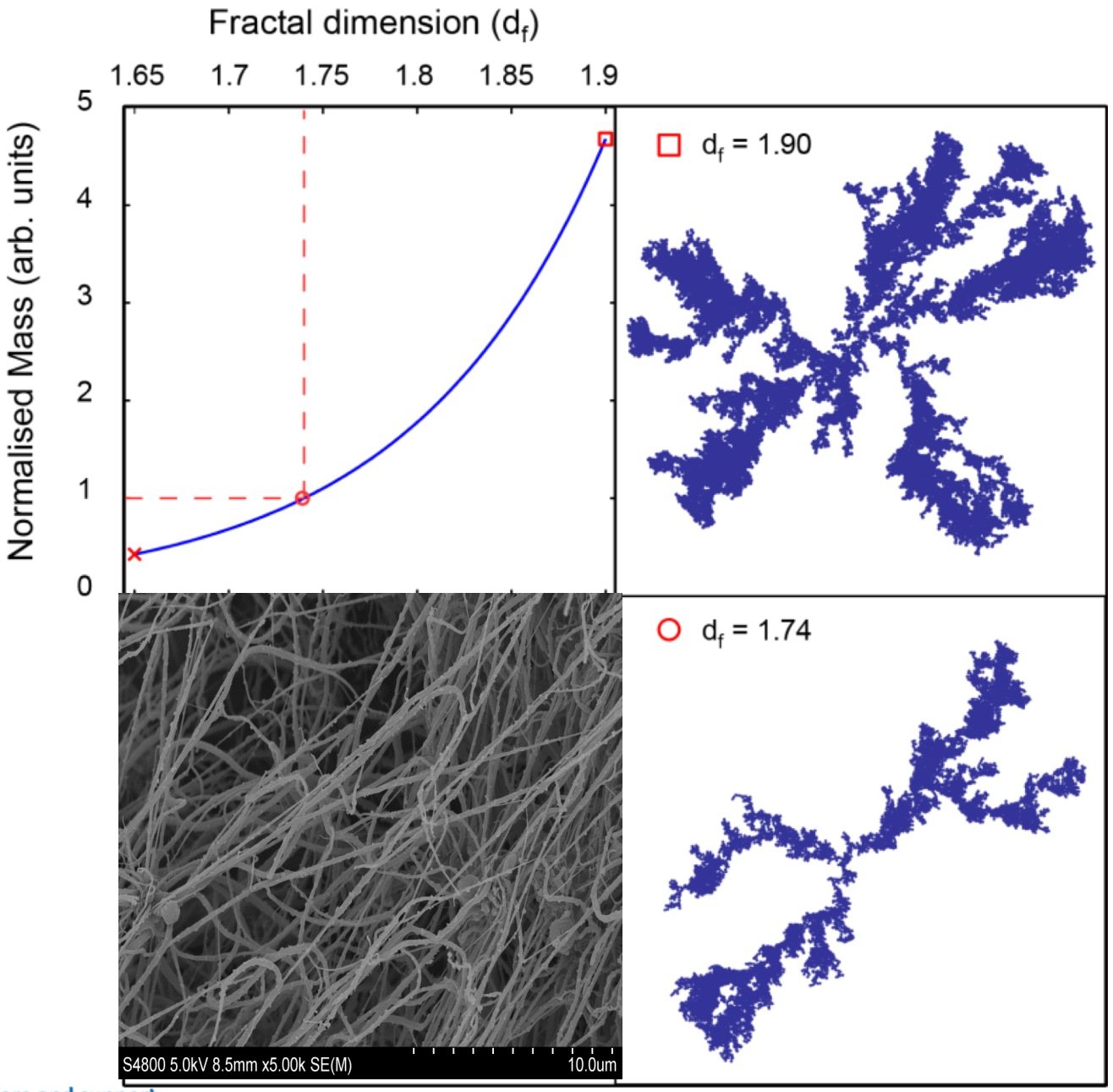

**Initiation**

**Propagation**

**Clot formation**



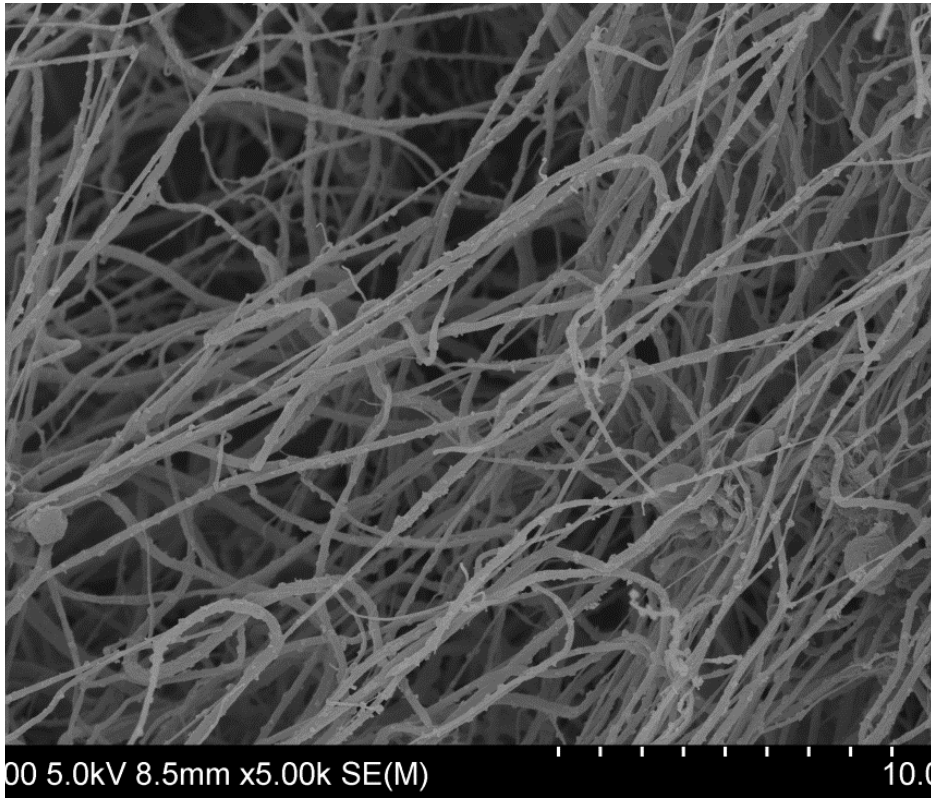





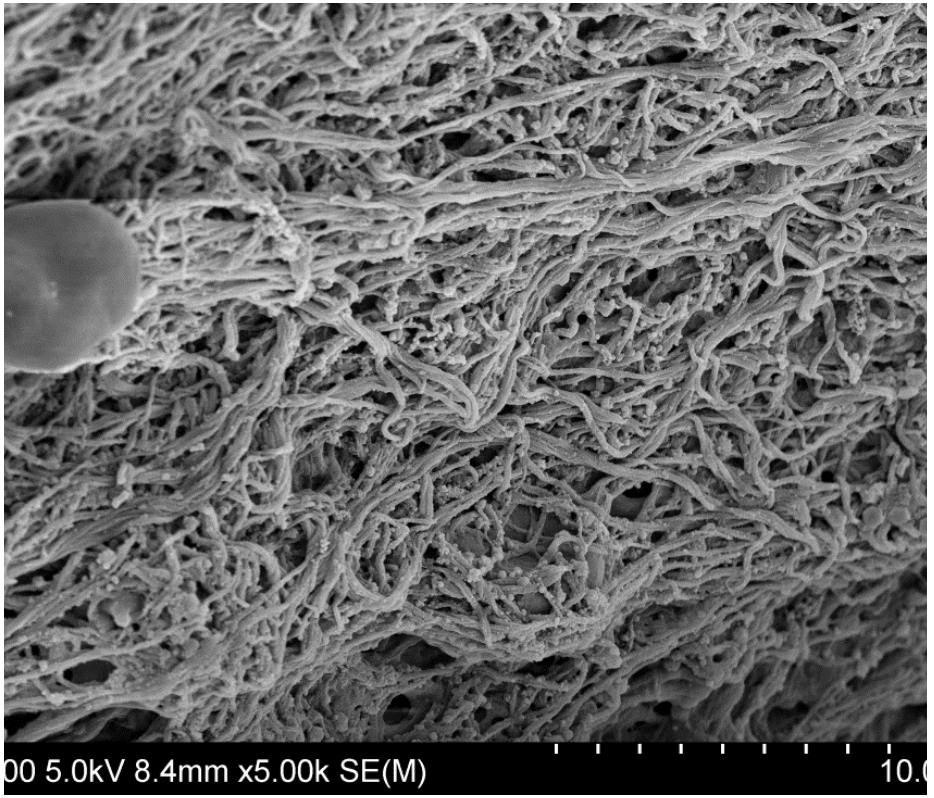

Lung cancer

Non-cancer

# Electron microscopy

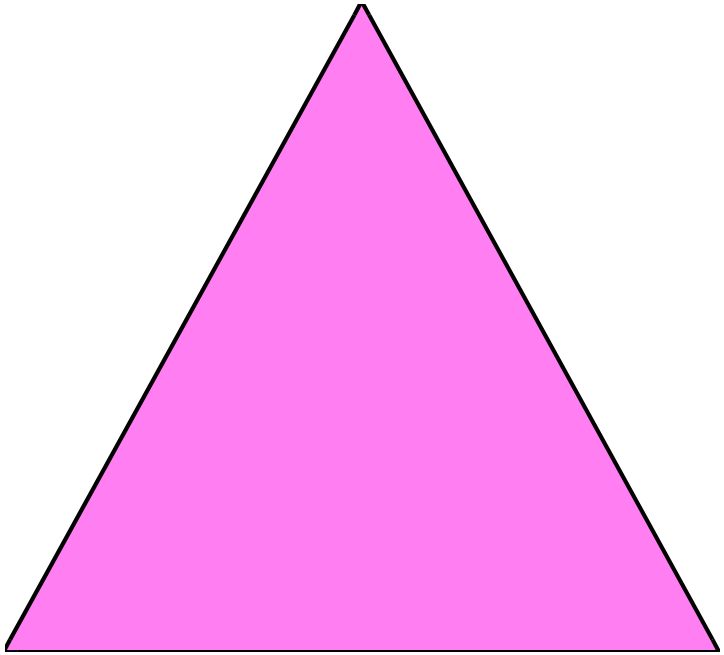


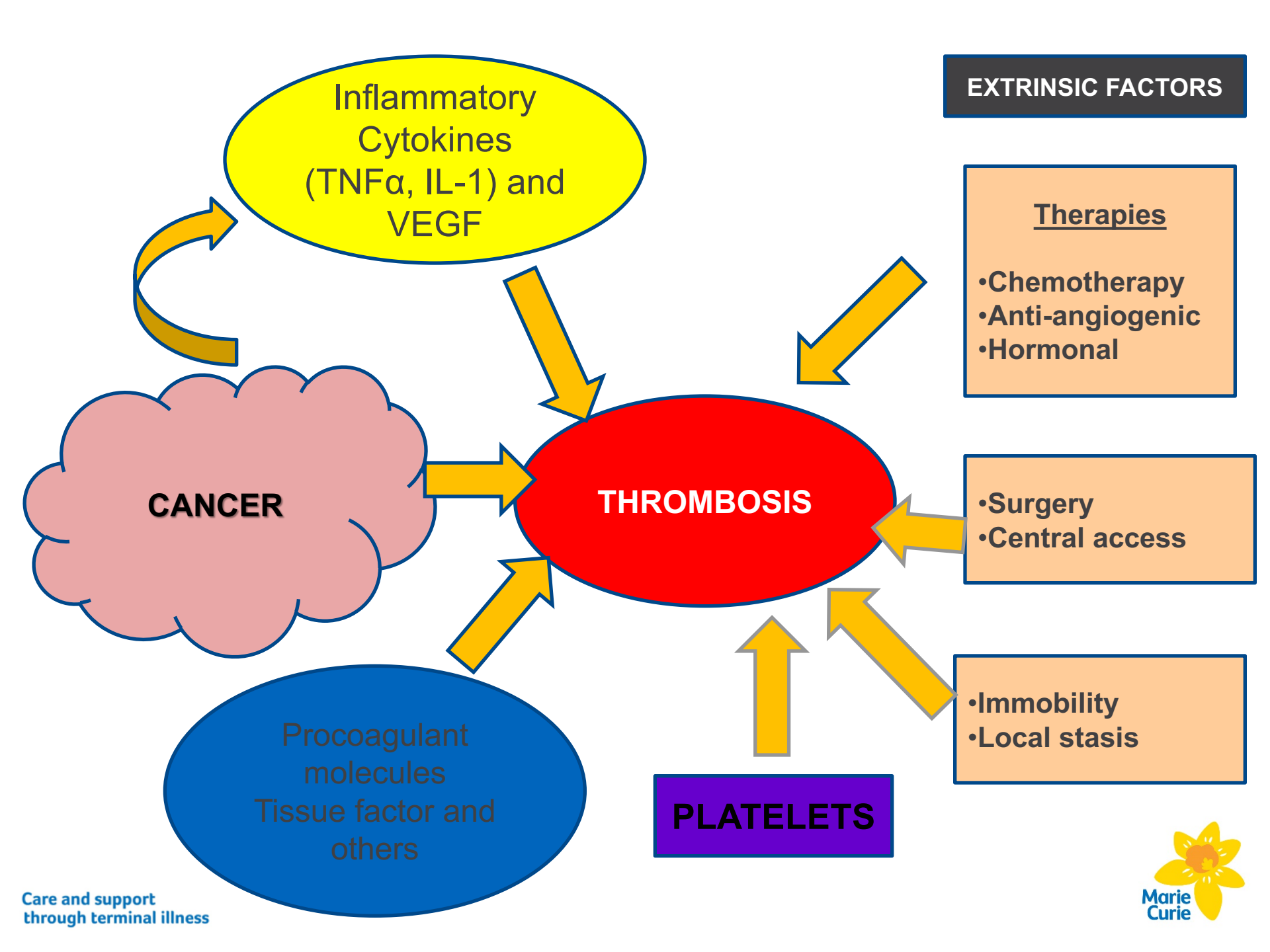

Healthy blood



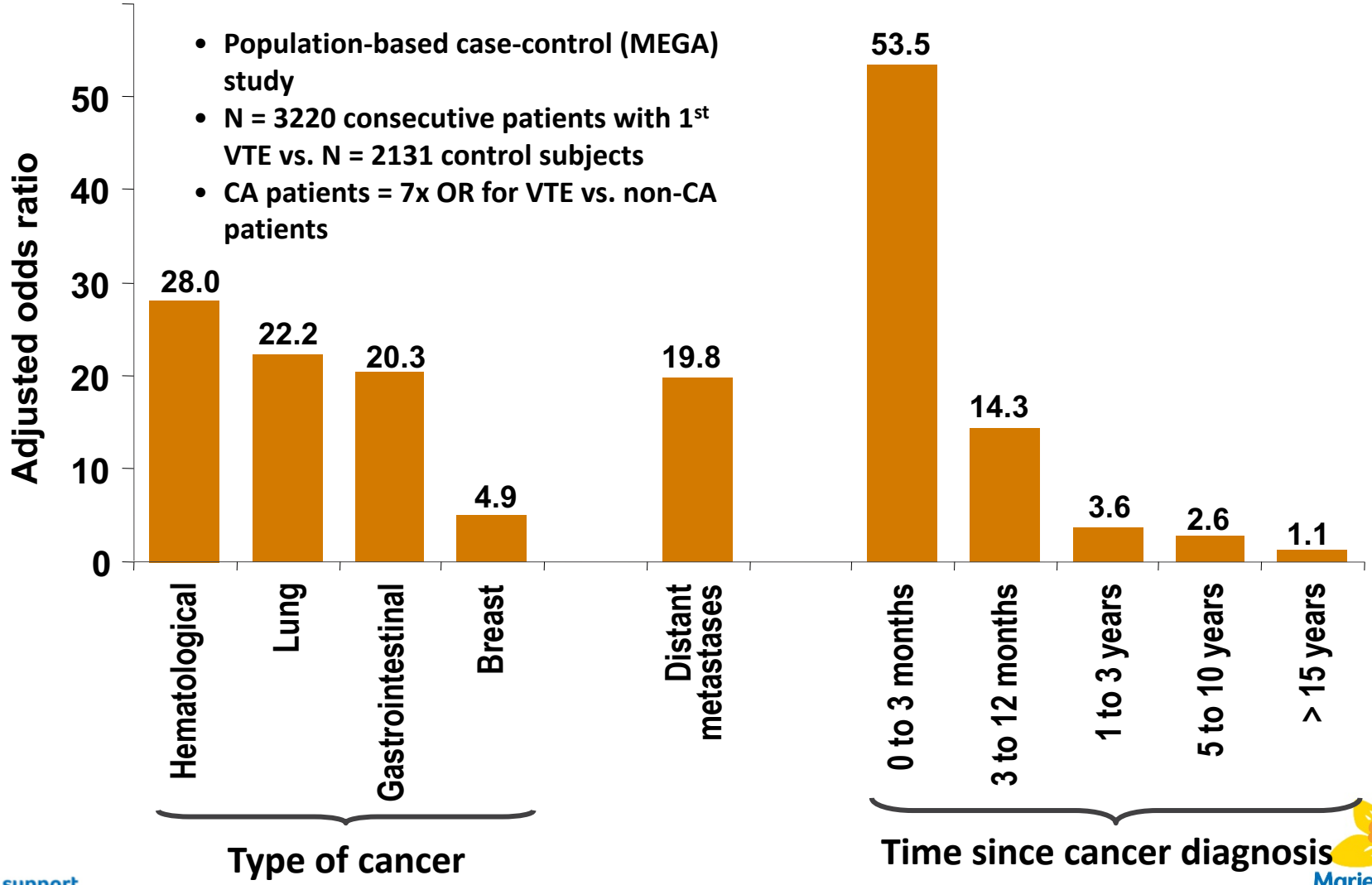

Blood from patient with stage IV lung cancer

# Virchow's triad




Inflammatory Cytokines (TNFα, IL-1) and VEGF
EXTRINSIC FACTORS
Therapies
•Chemotherapy
•Anti-angiogenic
•Hormonal
CANCER
THROMBOSIS
•Surgery
•Central access
Procoagulant molecules Tissue factor and others
PLATELETS
•Immobility
•Local stasis
Care and support through terminal illness
Marie Curie

# Effect of Malignancy on Risk of Venous Thromboembolism (VTE)

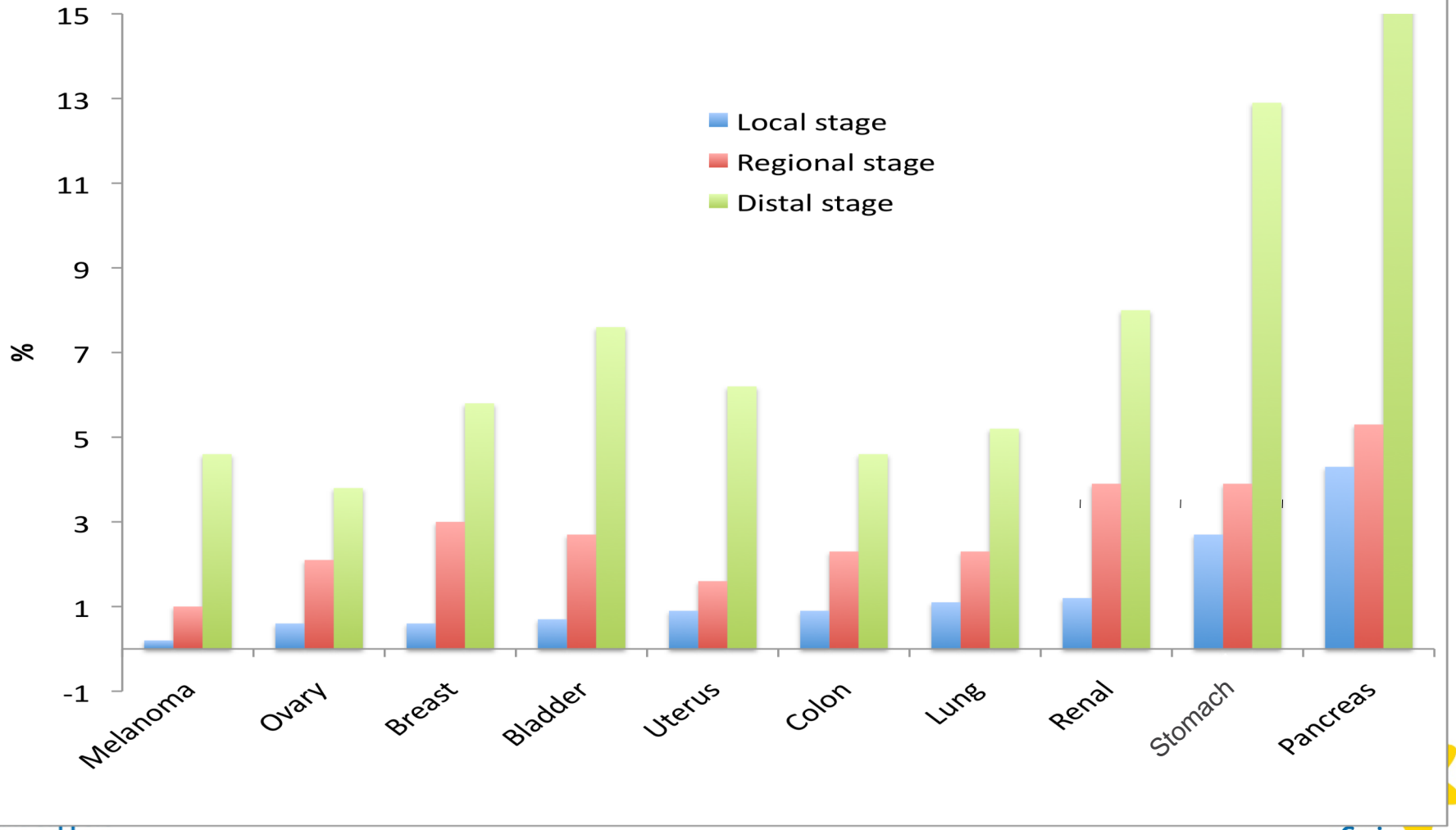



Care and support through terminal illness

Marie Curie

Silver *In:* The Hematologist - modified from Blom *et al. JAMA* 2005;293:715.

# Incidence of symptomatic CAT according to the cancer type and stage




through terminal illness

Curie

*Wun T, White RH. Best Pract Res Clin Haematol. 2009;22:9-23*

# Treatment impact on VTE Incidence In Various Tumors

| Oncology Setting | VTE Incidence |
|---|---|
| Breast cancer (Stage I & II) w/o further treatment | 0.2% |
| | |
| | |
| Advanced cancer (1-year survival=12%) | 9% |
| High-grade glioma | 26% |
| Multiple myeloma | 3-5% |
| | |
| Renal cell carcinoma | 43% |
| Solid tumors (anti-VEGF + chemo) | 47% |

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

# Treatment impact on VTE Incidence In Various Tumors

| Oncology Setting | VTE Incidence |
|---|---|
| Breast cancer (Stage I & II) w/o further treatment | 0.2% |
| Breast cancer (Stage I & II) w/ chemo | 2% |
| Breast cancer (Stage IV) w/ chemo | 8% |
| Advanced cancer (1-year survival=12%) | 9% |
| High-grade glioma | 26% |
| Multiple myeloma | 3-5% |
| | |
| Renal cell carcinoma | 43% |
| Solid tumors (anti-VEGF + chemo) | 47% |

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

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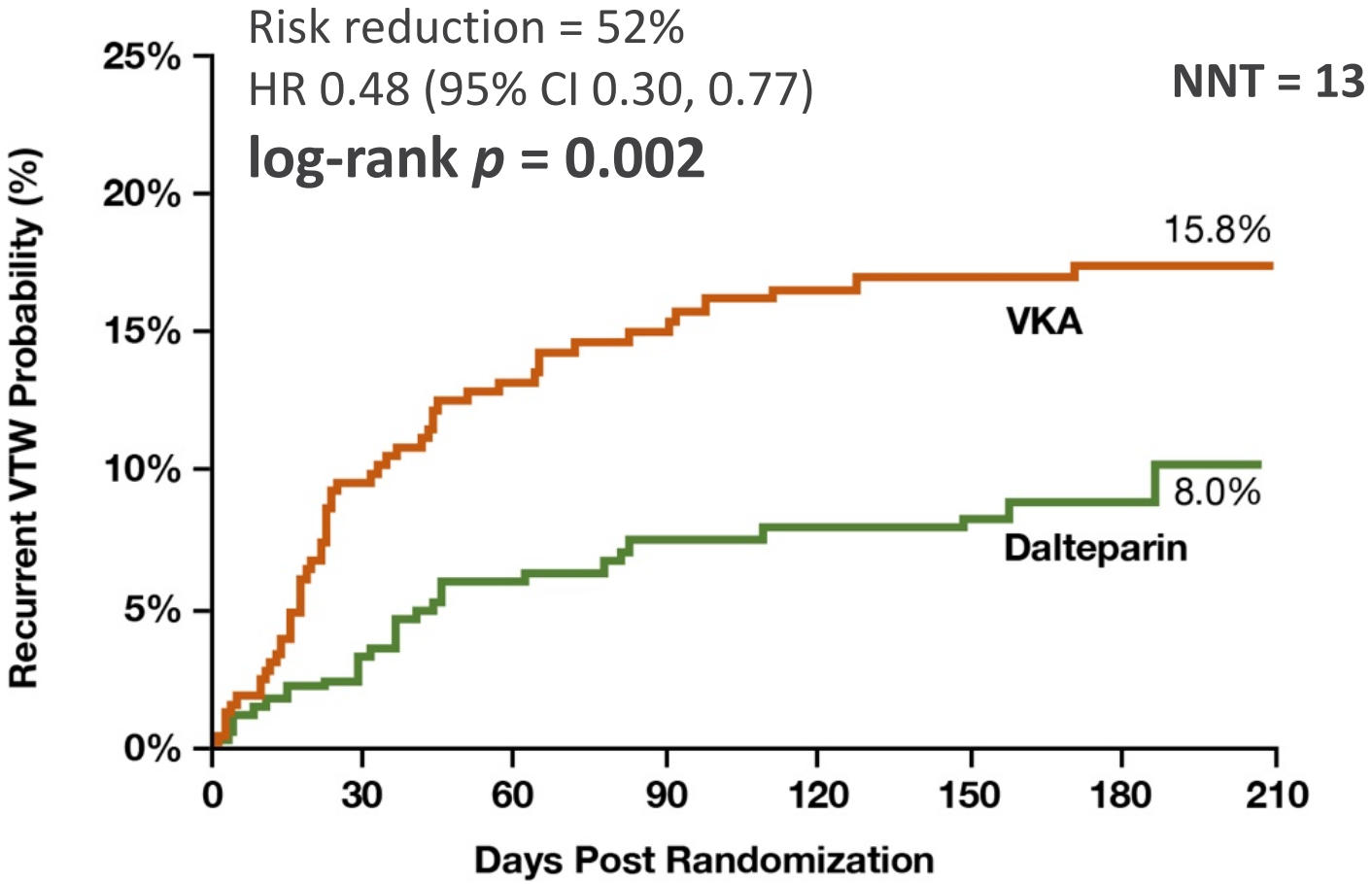
| Advanced cancer (1-year survival=12%) | 9% |
| High-grade glioma | 26% |
| Multiple myeloma | 3-5% |
| Multiple myeloma (thalidomide + chemo) | 28% |
| Renal cell carcinoma | 43% |
| Solid tumors (anti-VEGF + chemo) | 47% |

Otten, et al. Haemostasis 2000;30:72. Lee & Levine. Circulation 2003;107:I17

# The CLOT Trial
## *Primary outcome: VTE recurrence*

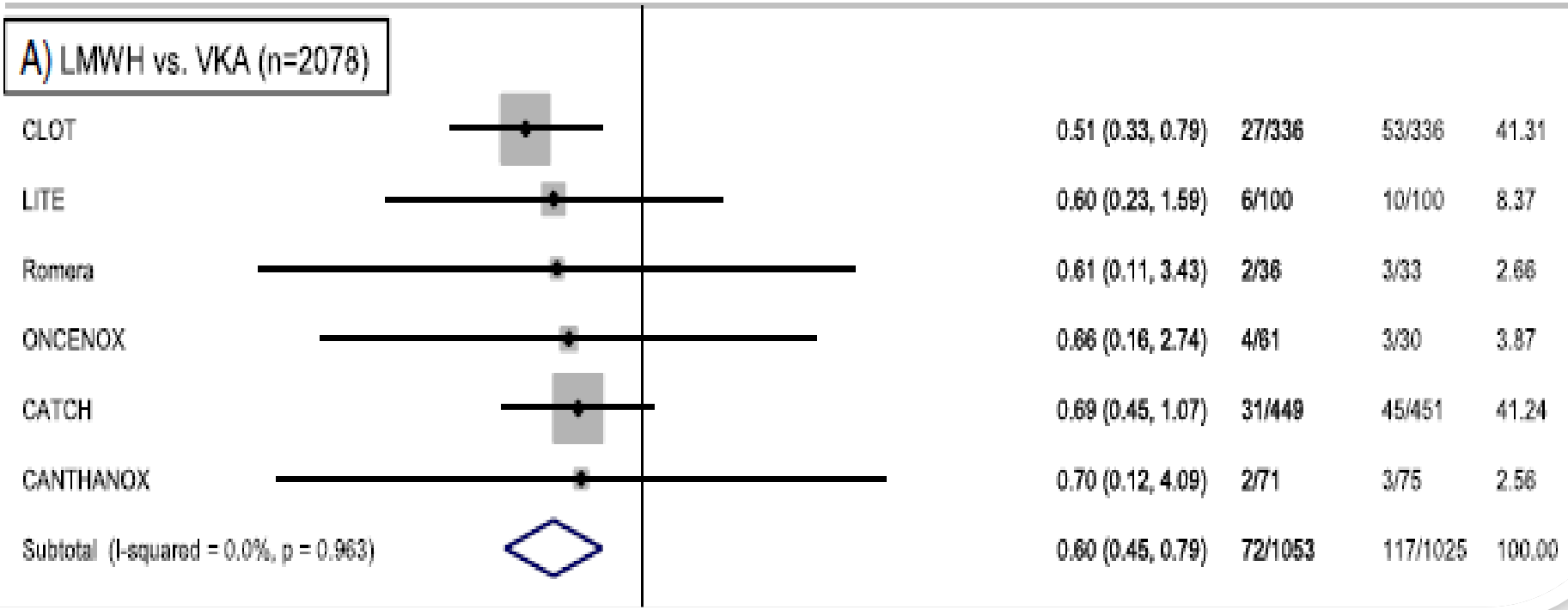



HR = hazard ratio; NNT = number needed to treat; VKA = vitamin K antagonist; VTE = venous thromboembolism



Lee AY *et al. N Engl J Med* 2003;349(2):146–153.

# LMWH vs warfarin meta analysis




Florian Posch et at, Thrombosis Research 136 (2015) 582–589

# Guideline recommendations

Guideline recommendations:

Standard of treatment for cancer-associated thrombosis is three to six months LMWH

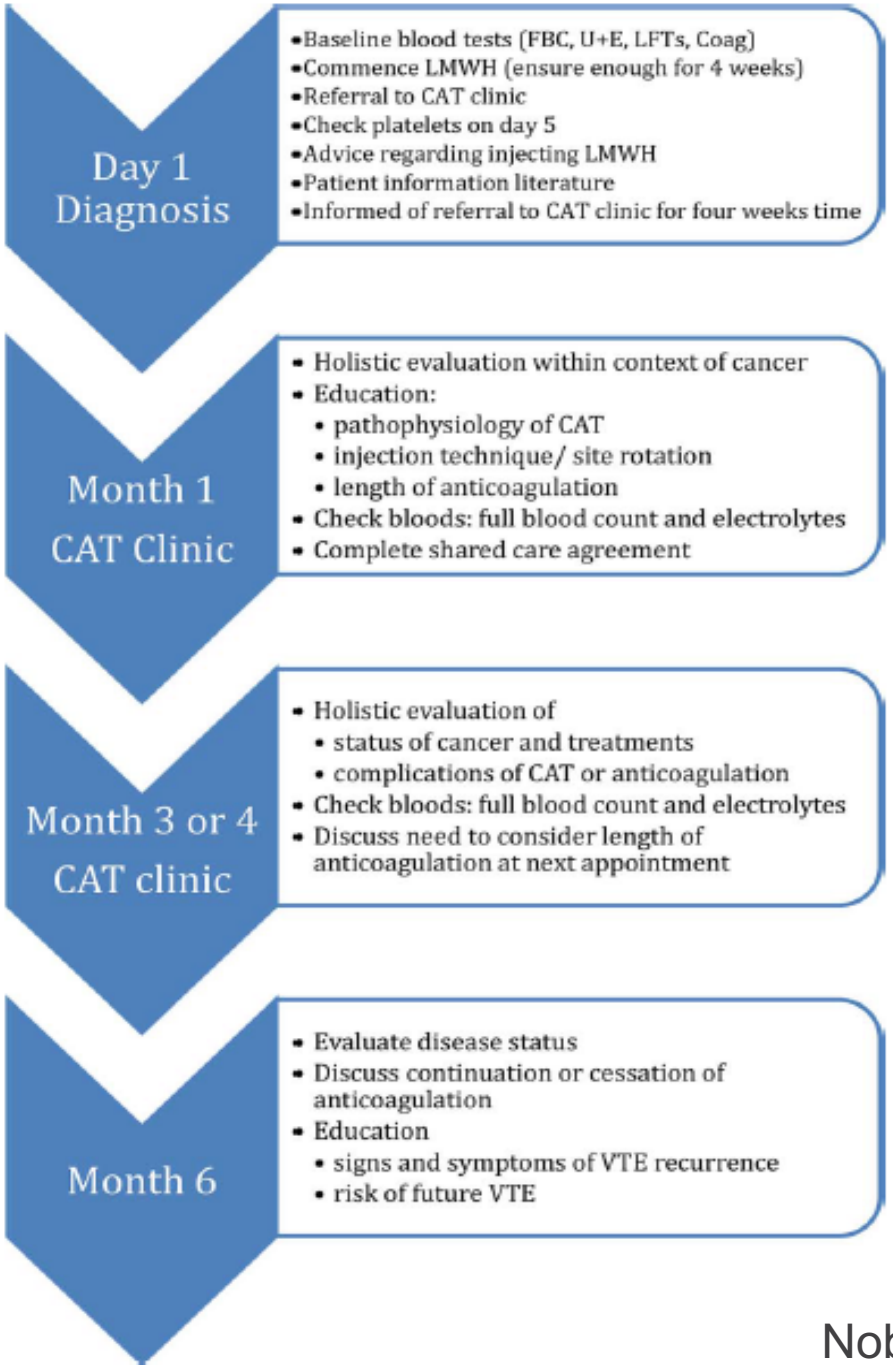
(Grade A)

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.

(Grade D)

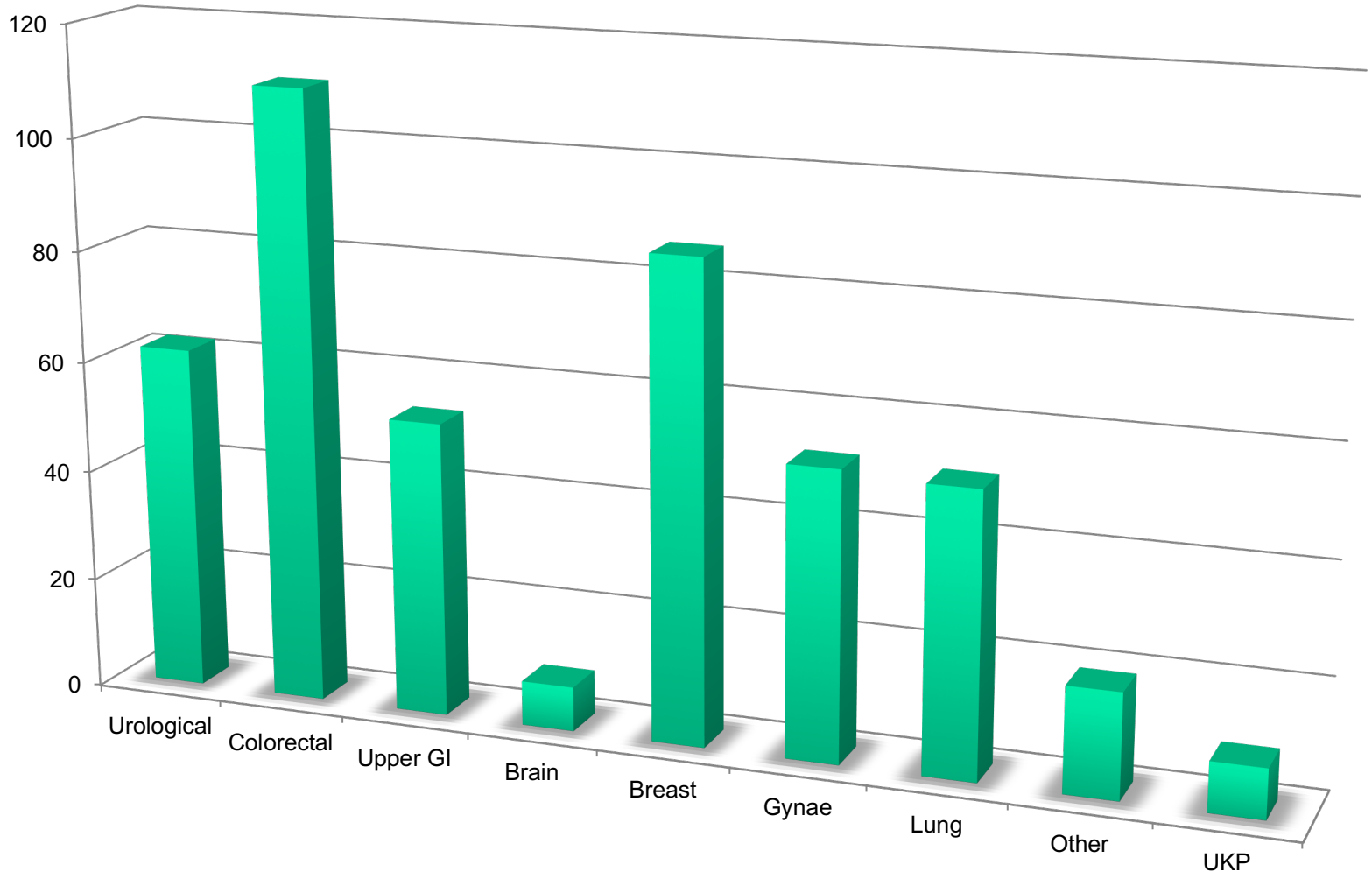
| | | |
|---|---|---|
| ISTH | LMWH | 3 to 6 months then VKA or LMWH until cancer resolution |

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist




Noble et al BMJ Open 2017

# Scope of patients



# Patient spread

44% metastatic

60% during chemotherapy (majority palliative)

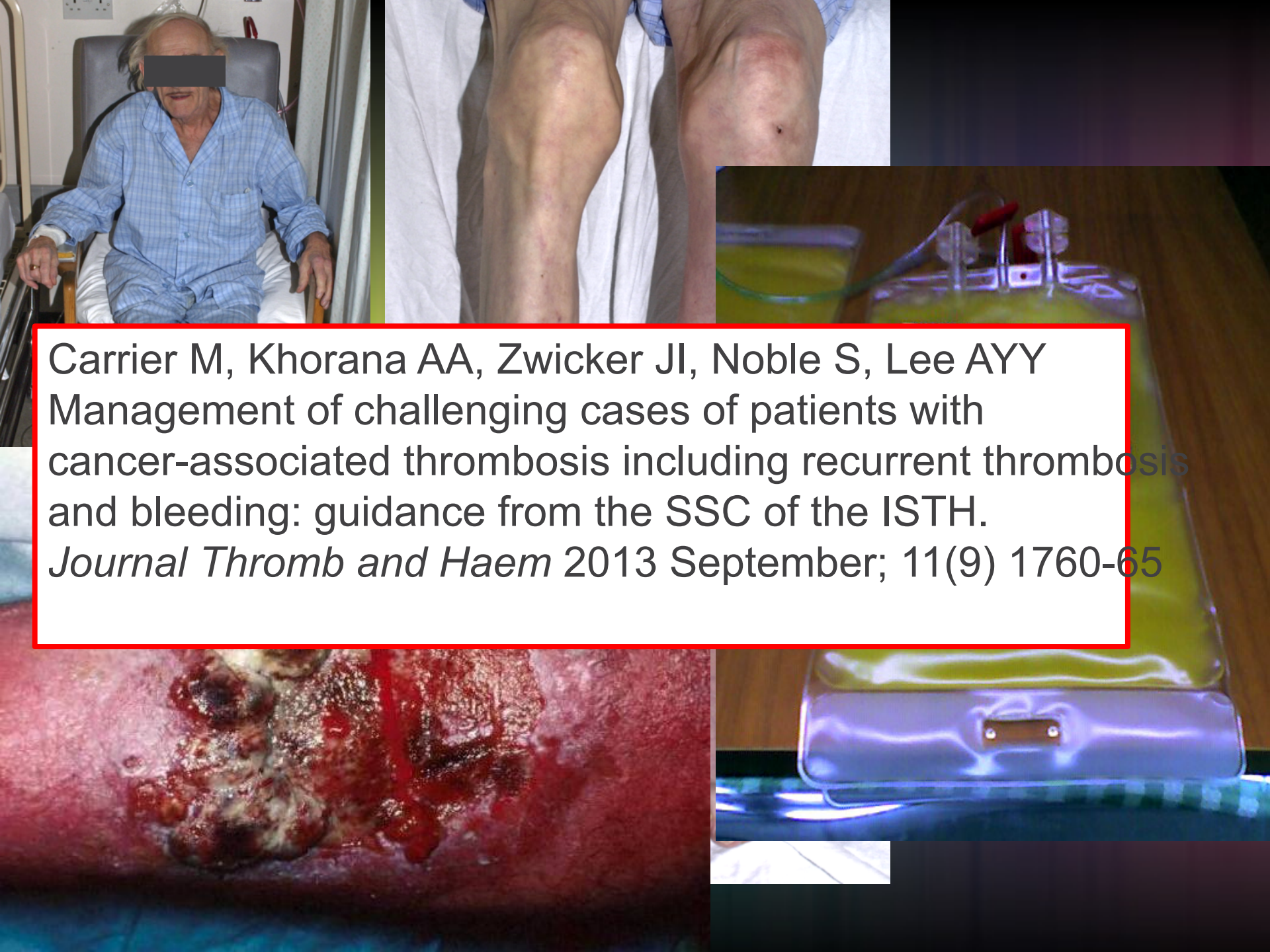
59% known to specialist palliative care services

# Need for specialist input

334 CLOT regime

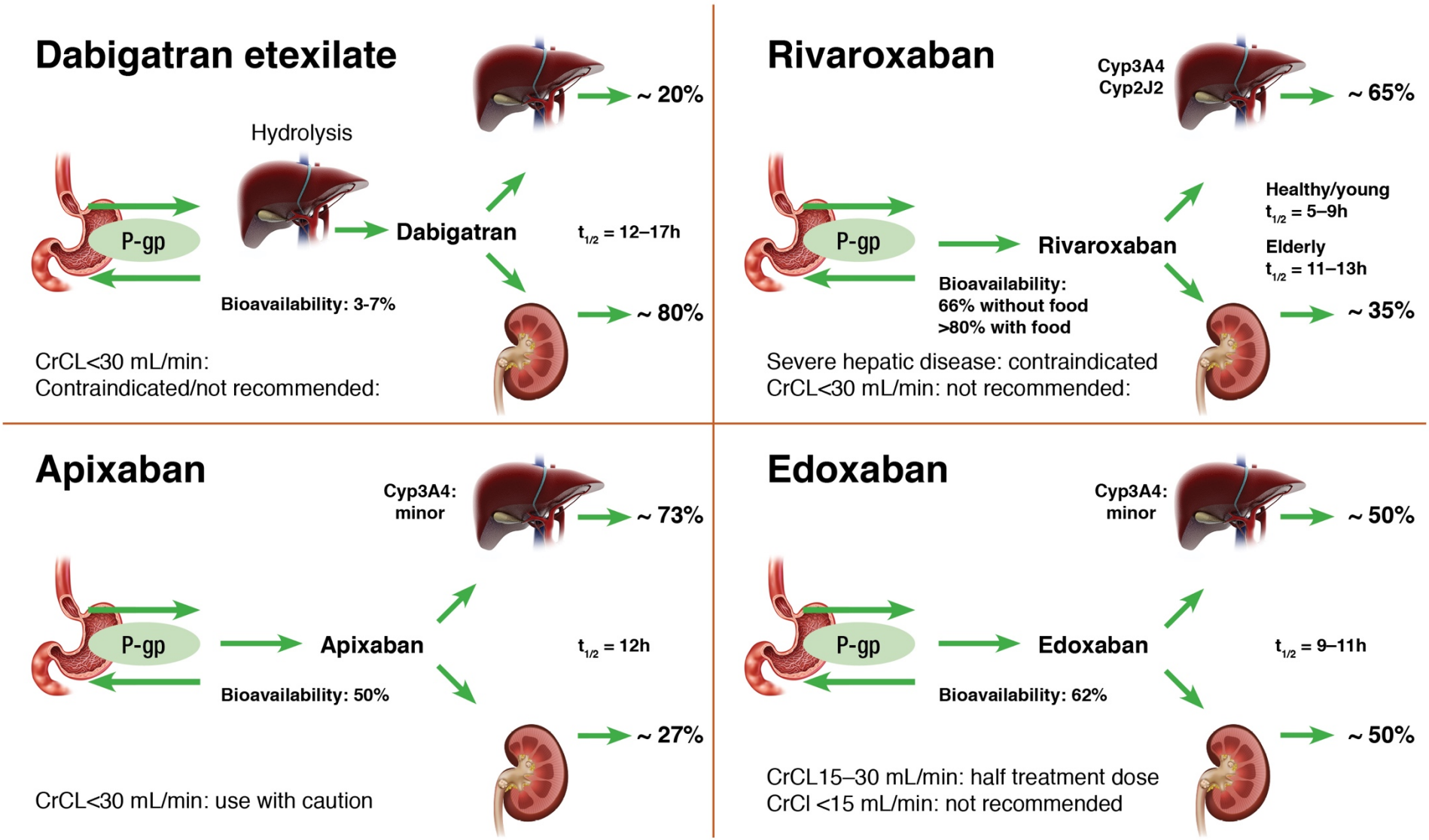
124 (27%) non CLOT

- Bleeding/ risk of bleeding
- Thrombus progression/ recurrence
- Renal impairment (EGFR<25)
- Intolerant injections
- Extremes of bodyweight



Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY
Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH.
*Journal Thromb and Haem* 2013 September; 11(9) 1760-65

# DOAC Pharmacology






Adapted from: Heidbuchel H *et al. Europace* 2013; U.S., Canadian Prescribing Information CrCl = creatinine clearance

# VTE treatment studies - new oral anticoagulants

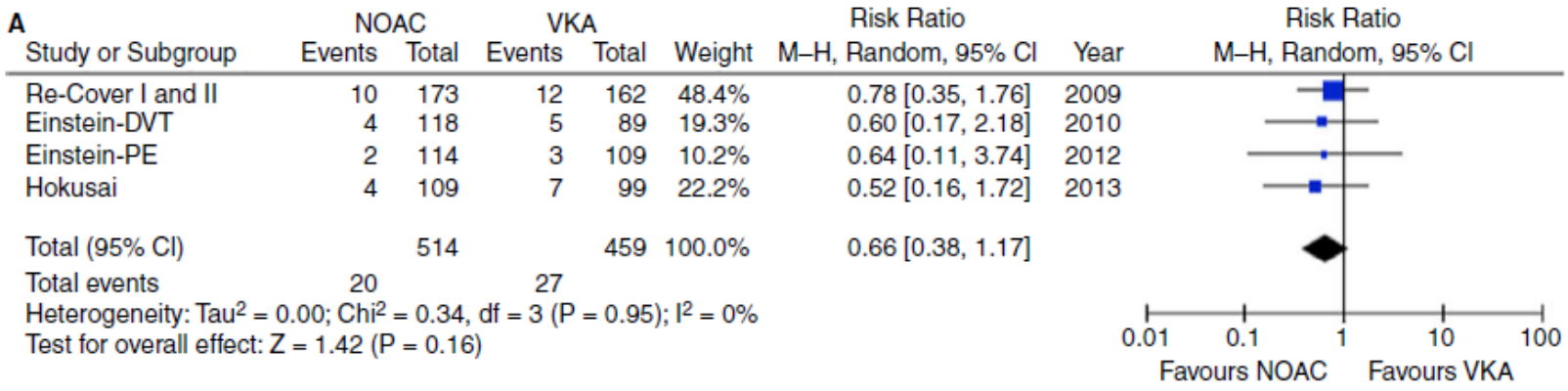
| | Hokusai-VTE | EINSTEIN-DVT<br>EINSTEIN-PE | AMPLIFY | RE-COVER I<br>RE-COVER II |
|---|---|---|---|---|
| **Drug** | Edoxaban▼ | Rivaroxaban▼ | Apixaban | Dabigatran |
| **Study design** | Double-blind | Open-label | Double-blind | Double-blind |
| **Heparin lead-in** | At least 5 days | None | None | At least 5 days |
| **Dose** | 60 mg qd<br>30 mg qd<br>(CrCl, bw, P-gp) | 15 mg bid x 3 wk<br>then 20 mg qd | 10 mg bid x 7 days then 5 mg bid | 150 mg bid |
| **Non-inferiority margin** | 1.5 | 2.0 | 1.8 | 2.75 |
| **Sample size** | 8,292 | **EINSTEIN-DVT**<br>3,449<br>**EINSTEIN-PE**<br>4,832 | 5,400 | **RE-COVER I**<br>2,564<br>**RE-COVER II**<br>2,568 |
| **Treatment duration** | Flexible<br>3 to 12 months | Pre-specified<br>3, 6, or 12 months | 6 months | 6 months |

Please note that there are no head to head RCTs between the NOACs. Results should not be directly compared because of important differences in the pharmacologic properties, the doses used, the patient populations, the quality of warfarin management or other aspects of the trial designs.

| RCT | Total studied population | Patients with cancer |
|---|---|---|
| EINSTEIN Acute DVT | **Rivaroxaban** = 1731<br>**Enox/VKA**= 1718 | **Rivaroxaban** = 6.8%<br>**Enox/VKA** = 5.2% |
| EINSTEIN DVT extension | **Rivaroxaban**= 602<br>**placebo**= 594 | **Rivaroxaban** = 4.5%<br>**Placebo** = 4.4% |
| EINSTEIN-PE | **Rivaroxaban**= 2419<br>**Enox/VKA**= 2413 | **Rivaroxaban** = 4.7%<br>**Enox/VKA**= 4.5% |
| RECOVER | **Dabigatran** = 1274<br>**VKA** = 1265 | **Dabigatran** = 5%<br>**VKA** = 4.5% |

# DOACs in the treatment of CAT

## Recurrent VTE



A

| Study or Subgroup | NOAC Events | NOAC Total | VKA Events | VKA Total | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Re-Cover I and II | 10 | 173 | 12 | 162 | 48.4% | 0.78 [0.35, 1.76] | 2009 |
| Einstein-DVT | 4 | 118 | 5 | 89 | 19.3% | 0.60 [0.17, 2.18] | 2010 |
| Einstein-PE | 2 | 114 | 3 | 109 | 10.2% | 0.64 [0.11, 3.74] | 2012 |
| Hokusai | 4 | 109 | 7 | 99 | 22.2% | 0.52 [0.16, 1.72] | 2013 |
| Total (95% CI) | | 514 | | 459 | 100.0% | 0.66 [0.38, 1.17] | |
| Total events | 20 | | 27 | | | | |

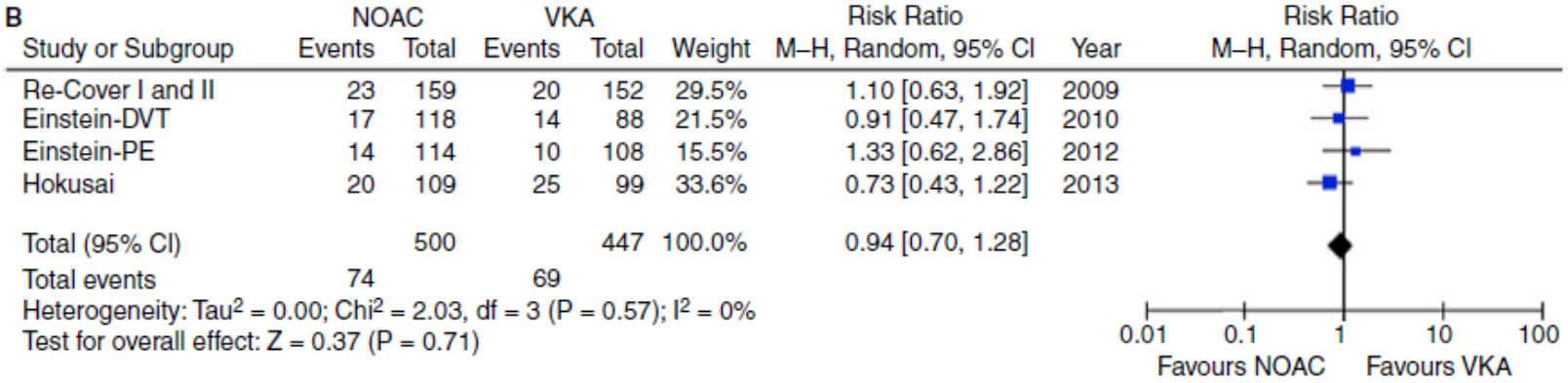
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 1.42 (P = 0.16)



Pooled incidence rates: 4.1% (2.6–6.0) for DOACs
6.1% (4.1–8.5) for VKAs [RR 0.66 (0.38–1.2)]

**Recurrent VTE warfarin**
Lee A *et al*. 2003: 16%
Meyer G *et al*. 2002 17%

## Major bleeding or CR-NMB



B

| Study or Subgroup | NOAC Events | NOAC Total | VKA Events | VKA Total | Weight | Risk Ratio M–H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Re-Cover I and II | 23 | 159 | 20 | 152 | 29.5% | 1.10 [0.63, 1.92] | 2009 |
| Einstein-DVT | 17 | 118 | 14 | 88 | 21.5% | 0.91 [0.47, 1.74] | 2010 |
| Einstein-PE | 14 | 114 | 10 | 108 | 15.5% | 1.33 [0.62, 2.86] | 2012 |
| Hokusai | 20 | 109 | 25 | 99 | 33.6% | 0.73 [0.43, 1.22] | 2013 |
| Total (95% CI) | | 500 | | 447 | 100.0% | 0.94 [0.70, 1.28] | |
| Total events | 74 | | 69 | | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, df = 3 (P = 0.57); $I^2 = 0\%$
Test for overall effect: Z = 0.37 (P = 0.71)



Care and through terminal illness

Curie

van der Hulle T *et al. J Thromb Haemost* 2014. CRNMB = clinically-relevant non-major bleeding

# Proportion of metastatic patients

| STUDY | LMWH | WARFARIN | RIVAROXABAN |
|---|---|---|---|
| CLOT | 66% | 69% | |
| LITE | 47% | 36% | |
| CATCH | 55% | 54% | |
| ONCENOX | 54% | 52% | |
| EINSTEIN DVT/PE | | 26% | 19% |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

## ABSTRACT

### BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

### METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

### RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

### CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

From the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam (N.E., H.R.B.), and ITREAS, Academic Research Organization (A.S.) — both in Amsterdam; the Department of Vascular Medicine and Hemostasis, University Hospitals Leuven, Leuven, Belgium (P.V.); Ottawa Hospital Research Institute, Ottawa (M.C.), London Health Sciences Centre–Victoria Hospital, London, ON (M.J.K.), University Health Network, University of Toronto, Toronto (E.Y.), and McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON (J.I.W.) — all in Canada; the Department of Medicine and Aging Sciences, University G. D'Annunzio, Chieti, Italy (M.D.N.); the Department of Medicine, Division of Hematology, University of Washington, Seattle (D.G.); Daiichi Sankyo Pharma Development, Basking Ridge, NJ (M.A.G., M.F.M., M.S., G.Z.); Thrombosis Research Institute and University College London, London (A.K.K.); the Department of Respiratory Diseases, Hôpital Européen Georges-Pompidou, Assistance Publique–Hôpitaux de Paris, Paris (G.M.); the Department of Internal Medicine, Division of Hematology, Ohio State University Wexner Medical Center, Columbus (T.-F.W.); and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (J.I.Z.). Address reprint requests to Dr. Raskob at the University of Oklahoma Health Sciences Center, College of Public Health, 801 NE 13th St., Oklahoma City, OK 73104, or at gary-raskob@ouhsc.edu.

*A complete list of Hokusai VTE Cancer Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Care and support through terminal illness

Marie Curie

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Care and support through terminal illness

Marie Curie

# Primary end point

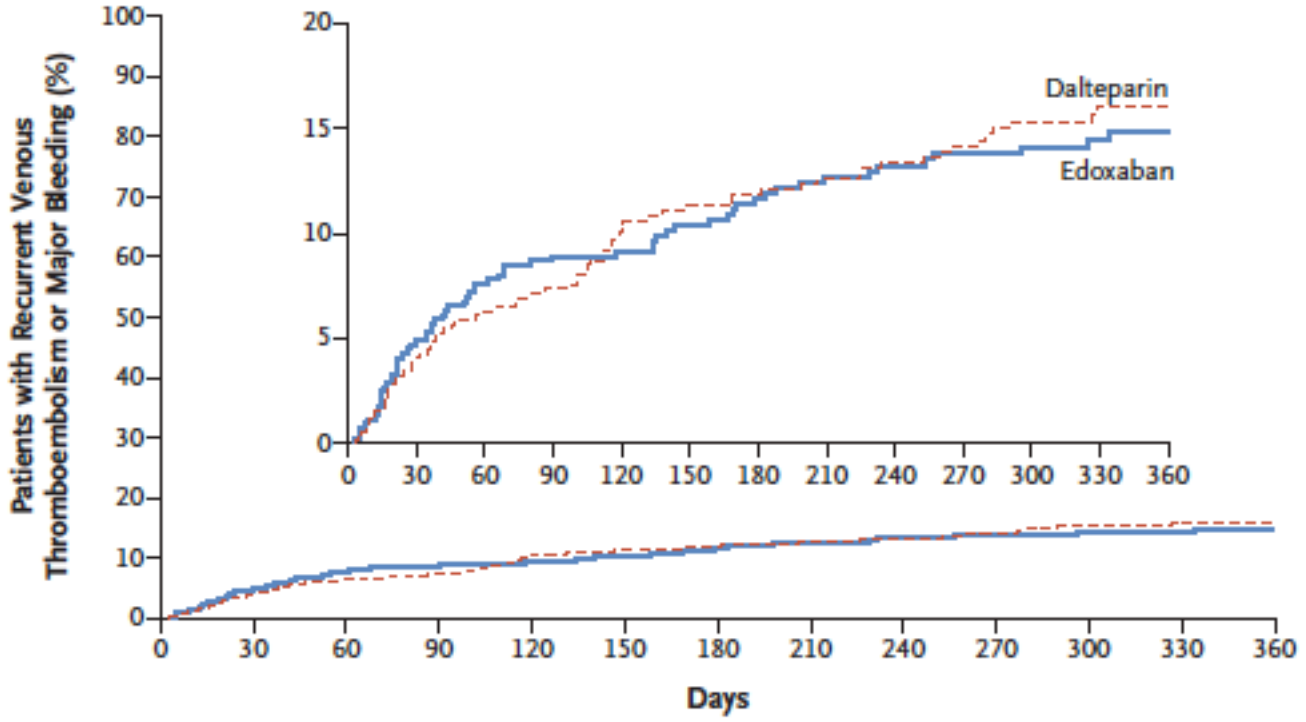
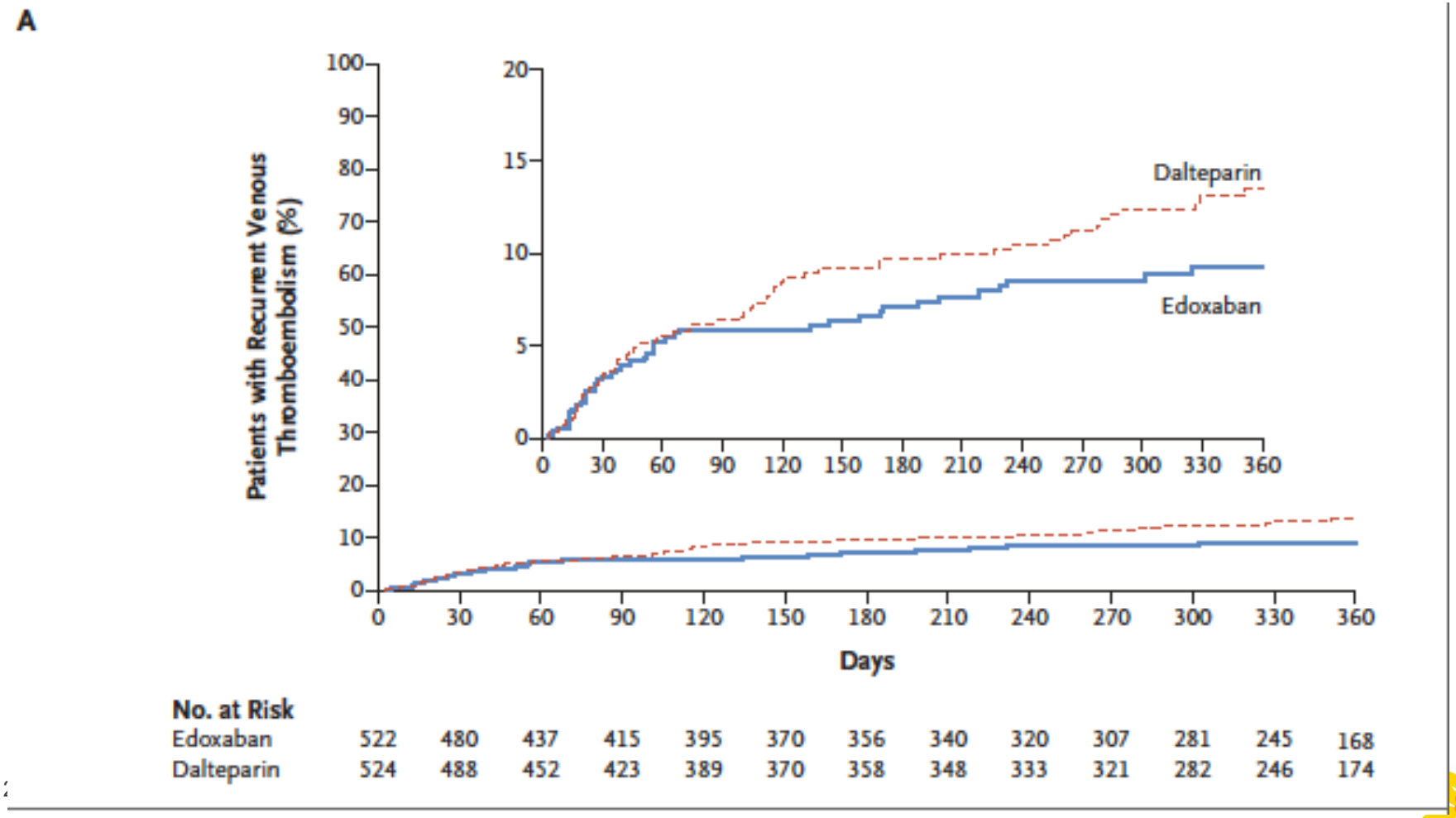



**Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.**

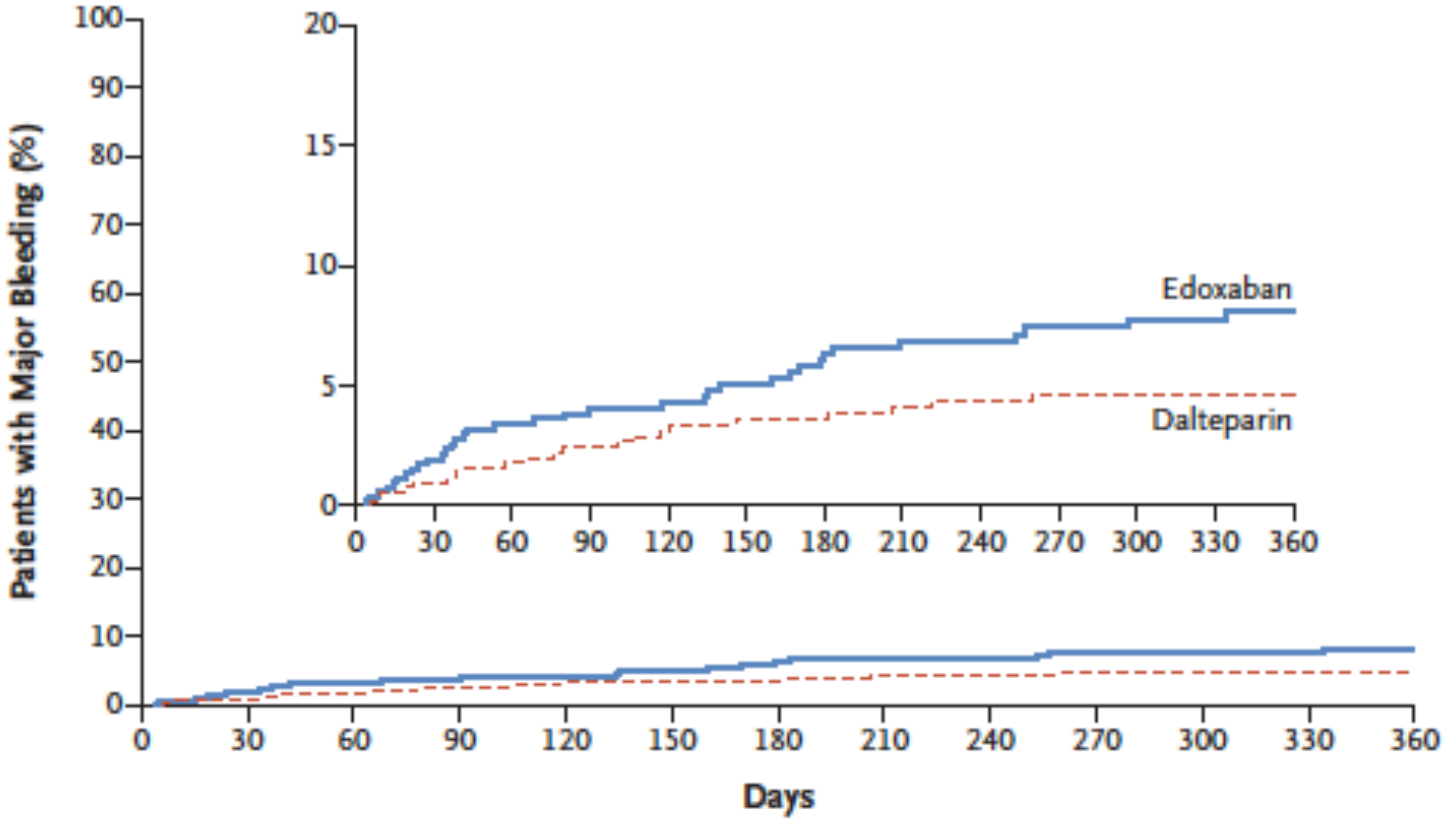
The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

# Recurrent VTE



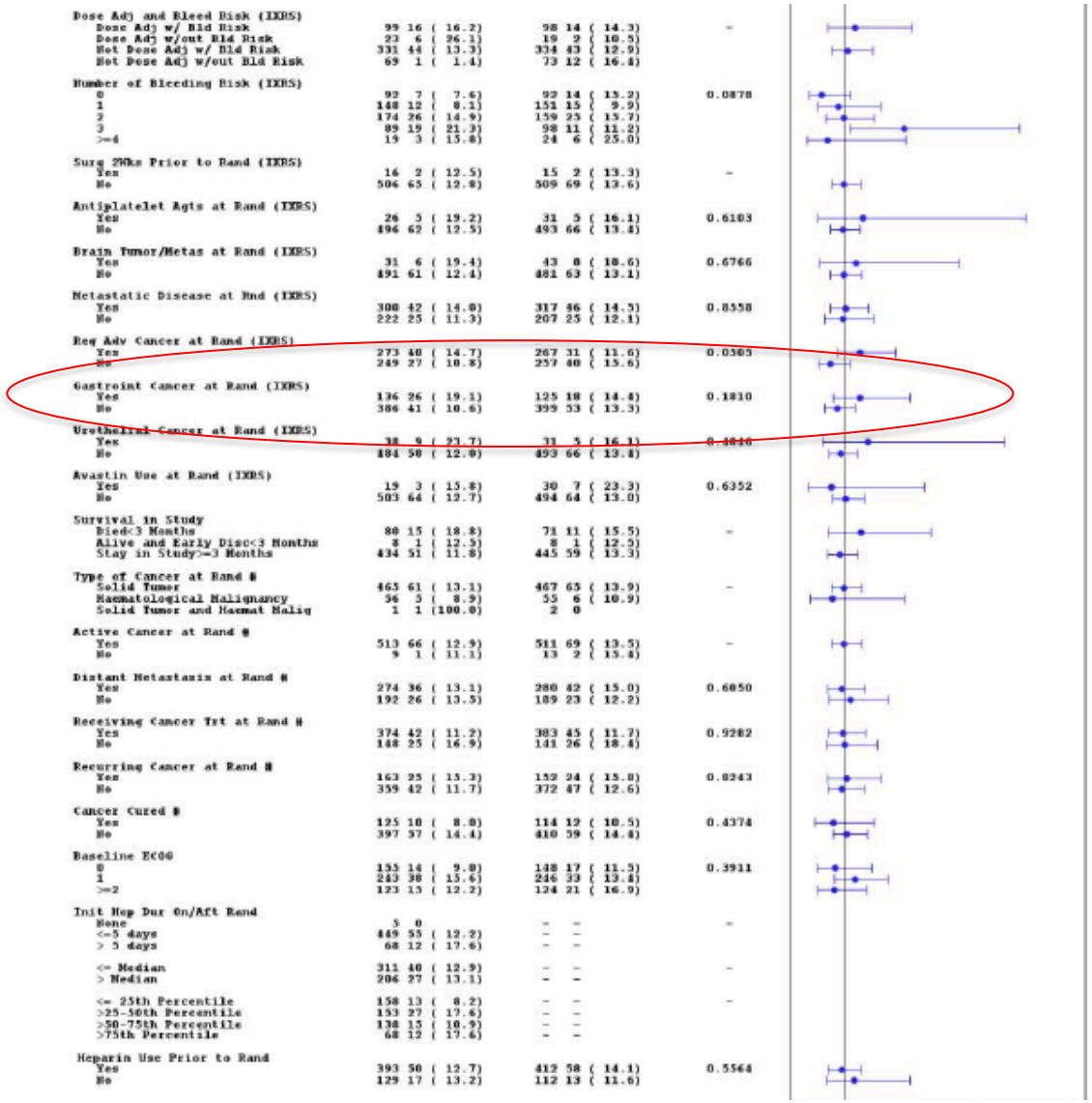
# Bleeding

B



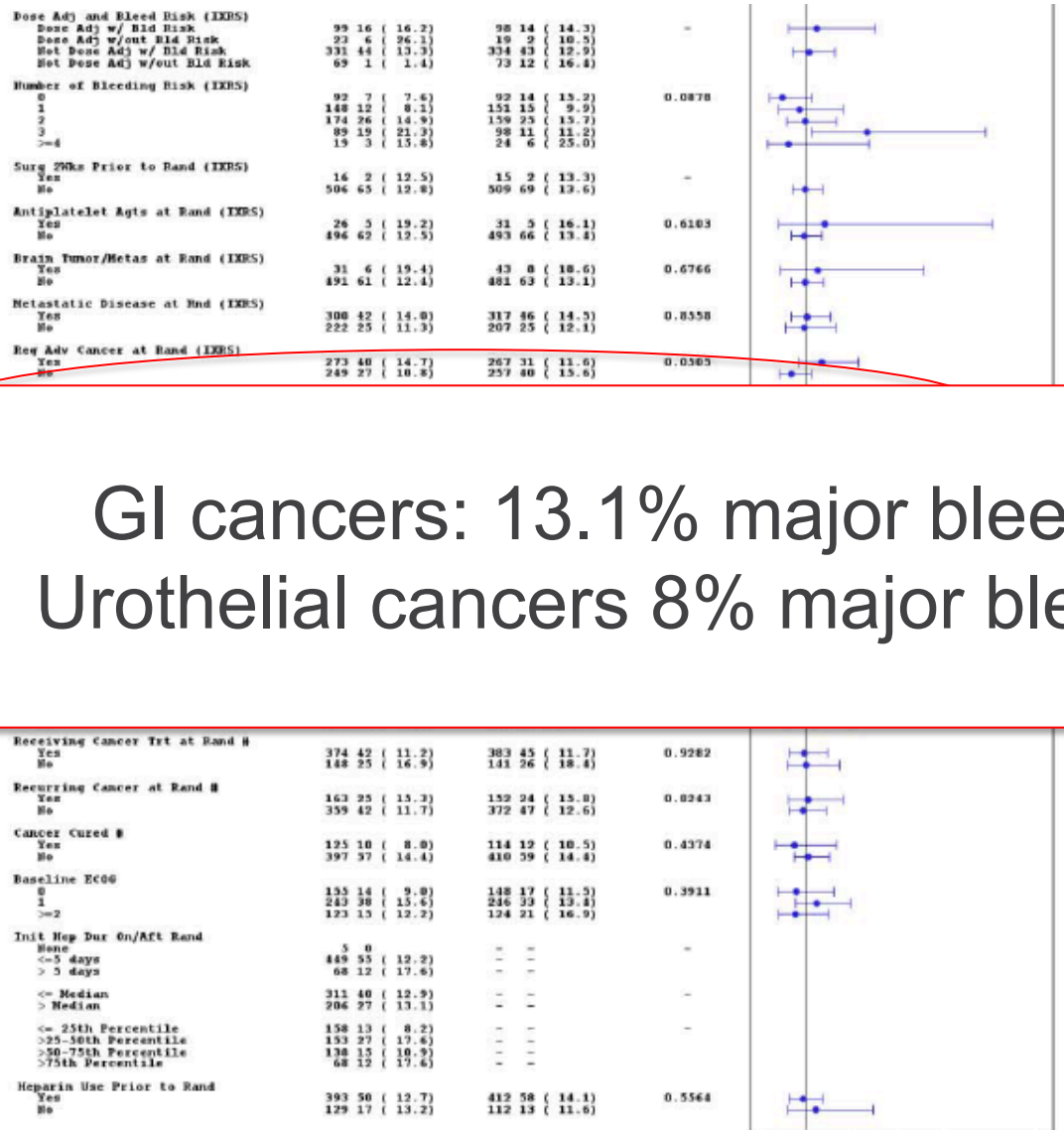

| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Edoxaban | 522 | 484 | 447 | 426 | 404 | 375 | 358 | 343 | 323 | 308 | 282 | 248 | 168 |
| Dalteparin | 524 | 497 | 466 | 436 | 409 | 390 | 378 | 356 | 346 | 335 | 298 | 262 | 183 |

# Appendix: page 16/32



| | | | |
|---|---|---|---|
| **Dose Adj and Bleed Risk (IXRS)** | | | |
| Dose Adj w/ Bld Risk | 99 16 ( 16.2) | 98 14 ( 14.3) | - |
| Dose Adj w/out Bld Risk | 22 6 ( 26.1) | 19 2 ( 10.5) | |
| Not Dose Adj w/ Bld Risk | 331 44 ( 13.3) | 334 43 ( 12.9) | |
| Not Dose Adj w/out Bld Risk | 69 1 ( 1.4) | 73 12 ( 16.4) | |
| **Number of Bleeding Risk (IXRS)** | | | |
| 0 | 92 7 ( 7.6) | 92 14 ( 15.2) | 0.0878 |
| 1 | 148 12 ( 8.1) | 151 15 ( 9.9) | |
| 2 | 174 26 ( 14.9) | 159 25 ( 15.7) | |
| 3 | 89 19 ( 21.3) | 98 11 ( 11.2) | |
| >=4 | 19 3 ( 15.8) | 24 6 ( 25.0) | |
| **Surg 2Wks Prior to Rand (IXRS)** | | | |
| Yes | 16 2 ( 12.5) | 15 2 ( 13.3) | - |
| No | 506 65 ( 12.8) | 509 69 ( 13.6) | |
| **Antiplatelet Agts at Rand (IXRS)** | | | |
| Yes | 26 5 ( 19.2) | 31 5 ( 16.1) | 0.6103 |
| No | 496 62 ( 12.5) | 493 66 ( 13.4) | |
| **Brain Tumor/Metas at Rand (IXRS)** | | | |
| Yes | 31 6 ( 19.4) | 43 8 ( 18.6) | 0.6766 |
| No | 491 61 ( 12.4) | 481 63 ( 13.1) | |
| **Metastatic Disease at Rnd (IXRS)** | | | |
| Yes | 308 42 ( 14.0) | 317 46 ( 14.5) | 0.8558 |
| No | 222 25 ( 11.3) | 207 25 ( 12.1) | |
| **Req Adv Cancer at Rand (IXRS)** | | | |
| Yes | 273 40 ( 14.7) | 267 31 ( 11.6) | 0.0305 |
| No | 249 27 ( 10.8) | 257 40 ( 15.6) | |
| **Gastroint Cancer at Rand (IXRS)** | | | |
| Yes | 136 26 ( 19.1) | 125 18 ( 14.4) | 0.1810 |
| No | 386 41 ( 10.6) | 399 53 ( 13.3) | |
| **Urothelial Cancer at Rand (IXRS)** | | | |
| Yes | 38 9 ( 23.7) | 31 5 ( 16.1) | 0.4016 |
| No | 484 58 ( 12.0) | 493 66 ( 13.4) | |
| **Avastin Use at Rand (IXRS)** | | | |
| Yes | 19 3 ( 15.8) | 30 7 ( 23.3) | 0.6352 |
| No | 503 64 ( 12.7) | 494 64 ( 13.0) | |
| **Survival in Study** | | | |
| Died<3 Months | 80 15 ( 18.8) | 71 11 ( 15.5) | - |
| Alive and Early Disc<3 Months | 8 1 ( 12.5) | 8 1 ( 12.5) | |
| Stay in Study>=3 Months | 434 51 ( 11.8) | 445 59 ( 13.3) | |
| **Type of Cancer at Rand #** | | | |
| Solid Tumor | 465 61 ( 13.1) | 467 65 ( 13.9) | - |
| Haematological Malignancy | 56 5 ( 8.9) | 55 6 ( 10.9) | |
| Solid Tumor and Haemat Malig | 1 1 (100.0) | 2 0 | |
| **Active Cancer at Rand #** | | | |
| Yes | 513 66 ( 12.9) | 511 69 ( 13.5) | - |
| No | 9 1 ( 11.1) | 13 2 ( 15.4) | |
| **Distant Metastasis at Rand #** | | | |
| Yes | 274 36 ( 13.1) | 280 42 ( 15.0) | 0.6050 |
| No | 192 26 ( 13.5) | 189 23 ( 12.2) | |
| **Receiving Cancer Trt at Rand #** | | | |
| Yes | 374 42 ( 11.2) | 383 45 ( 11.7) | 0.9282 |
| No | 148 25 ( 16.9) | 141 26 ( 18.4) | |
| **Recurring Cancer at Rand #** | | | |
| Yes | 163 25 ( 15.3) | 152 24 ( 15.8) | 0.8243 |
| No | 359 42 ( 11.7) | 372 47 ( 12.6) | |
| **Cancer Cured #** | | | |
| Yes | 125 10 ( 8.0) | 114 12 ( 10.5) | 0.4374 |
| No | 397 57 ( 14.4) | 410 59 ( 14.4) | |
| **Baseline ECOG** | | | |
| 0 | 155 14 ( 9.0) | 148 17 ( 11.5) | 0.3911 |
| 1 | 243 38 ( 15.6) | 246 33 ( 13.4) | |
| >=2 | 123 15 ( 12.2) | 124 21 ( 16.9) | |
| **Init Hep Dur On/Aft Rand** | | | |
| None | 5 0 | - - | - |
| <=5 days | 449 55 ( 12.2) | - - | |
| > 5 days | 68 12 ( 17.6) | - - | |
| <= Median | 311 40 ( 12.9) | - - | - |
| > Median | 206 27 ( 13.1) | - - | |
| <= 25th Percentile | 158 13 ( 8.2) | - - | - |
| >25-50th Percentile | 153 27 ( 17.6) | - - | |
| >50-75th Percentile | 138 15 ( 10.9) | - - | |
| >75th Percentile | 68 12 ( 17.6) | - - | |
| **Heparin Use Prior to Rand** | | | |
| Yes | 393 50 ( 12.7) | 412 58 ( 14.1) | 0.5564 |
| No | 129 17 ( 13.2) | 112 13 ( 11.6) | |

# Appendix: page 16/32




GI cancers: 13.1% major bleeding
Urothelial cancers 8% major bleeding

# Select-D

**Rivaroxaban vs dalteparin**

**400 patients: 90% metastatic disease, 83% chemo**

**4% vs 11% (95% CI 7-17%) recurrent VTE**

**4% vs 3% major bleeds**

**11% vs 2% CRNMB**

# *Drug interations*

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| **Interaction effect*** | P-glycoprotein | P-glycoprotein<br>CYP3A4 | P-glycoprotein<br>CYP3A4 | P-glycoprotein |
| **Increases DOAC plasma levels†** | Cyclosporine | Cyclosporine | Cyclosporine | Cyclosporine |
| | Tacrolimus | Tacrolimus | Tacrolimus | Tacrolimus |
| | Tamoxifen | Tamoxifen | Tamoxifen | Tamoxifen |
| | Lapatinib | Lapatinib | Lapatinib | Lapatinib |
| | Nilotinib | Nilotinib | Nilotinib | Nilotinib |
| | Sunitinib | Sunitinib | Sunitinib | Sunitinib |
| | | Imatinib | Imatinib | |
| **Reduces DOAC plasma levels‡** | Dexamethasone | Dexamethasone | Dexamethasone | Dexamethasone |
| | Doxorubicin | Doxorubicin | Doxorubicin | Doxorubicin |
| | Vinblastine | Vinblastine | Vinblastine | Vinblastine |

*Clinicians should consult pharmacist; †Drugs that inhibit P-GP or CYP3A4 can increase DOAC levels; ‡Drugs that induce P-GP or CYP3A4 can lower DOAC levels.

CYP3A4 = cytochrome P450 3A4; DOAC = direct oral anticoagulant



Lee, AY, Peterson EA. *Blood* 2013.

# Special circumstances

| | LMWH | DOACs |
|---|---|---|
| Extremes of body weight | Commonly used | Not recommended |
| Chemotherapy | Few drug-drug interactions | Avoid in strong inducers/ inhibitors of p-GP or CYP3A4 |
| Renal impairment | Dose adjustment | Dose adjustment |
| Thrombocytopenia | Dose adjustment | Dose adjustment |

| | LMWH | DOACs |
|---|---|---|
| Heparin induced thrombocytopenia | Contraindicated | Not contraindicated |
| Upper GI/ urothelial cancers | Commonly used | Increased bleeding risk: avoid |
| Needle phobia | Not advised | Acceptable |
| Liver disease | Used with caution | Used with caution |

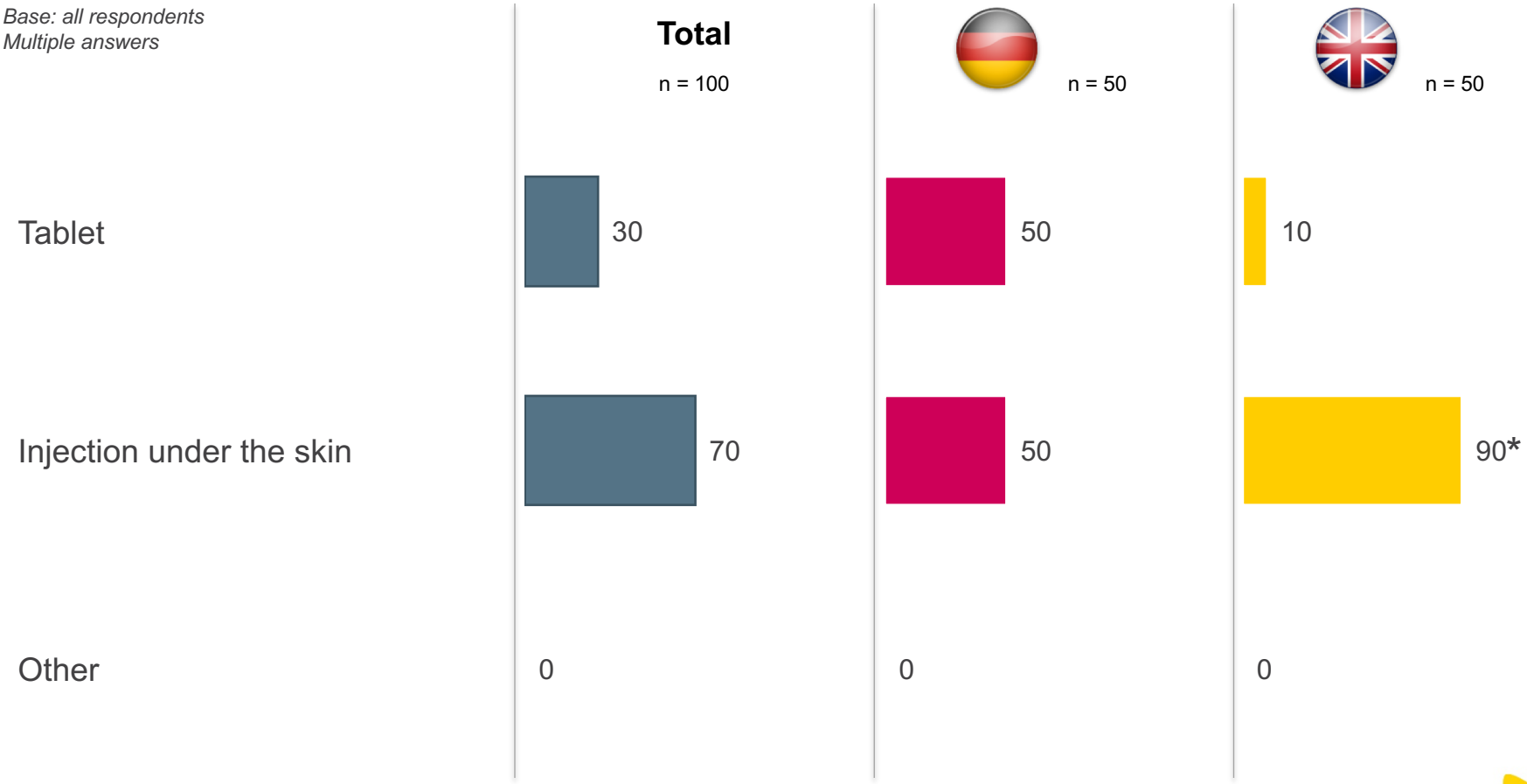
# Renal impairment

| | Apixaban | Edoxaban | Dabigatran | Rivaroxaban |
|---|---|---|---|---|
| Renal Clearance | 27% | 50% | 80% | 35% |
| CrCL <30ml/min | Use with caution | Dose reduction | Do not use | Do not use |

# Around one third of patients are currently treated with oral medication for their VTE

**Administration of medication (%)**

*Base: all respondents*
*Multiple answers*



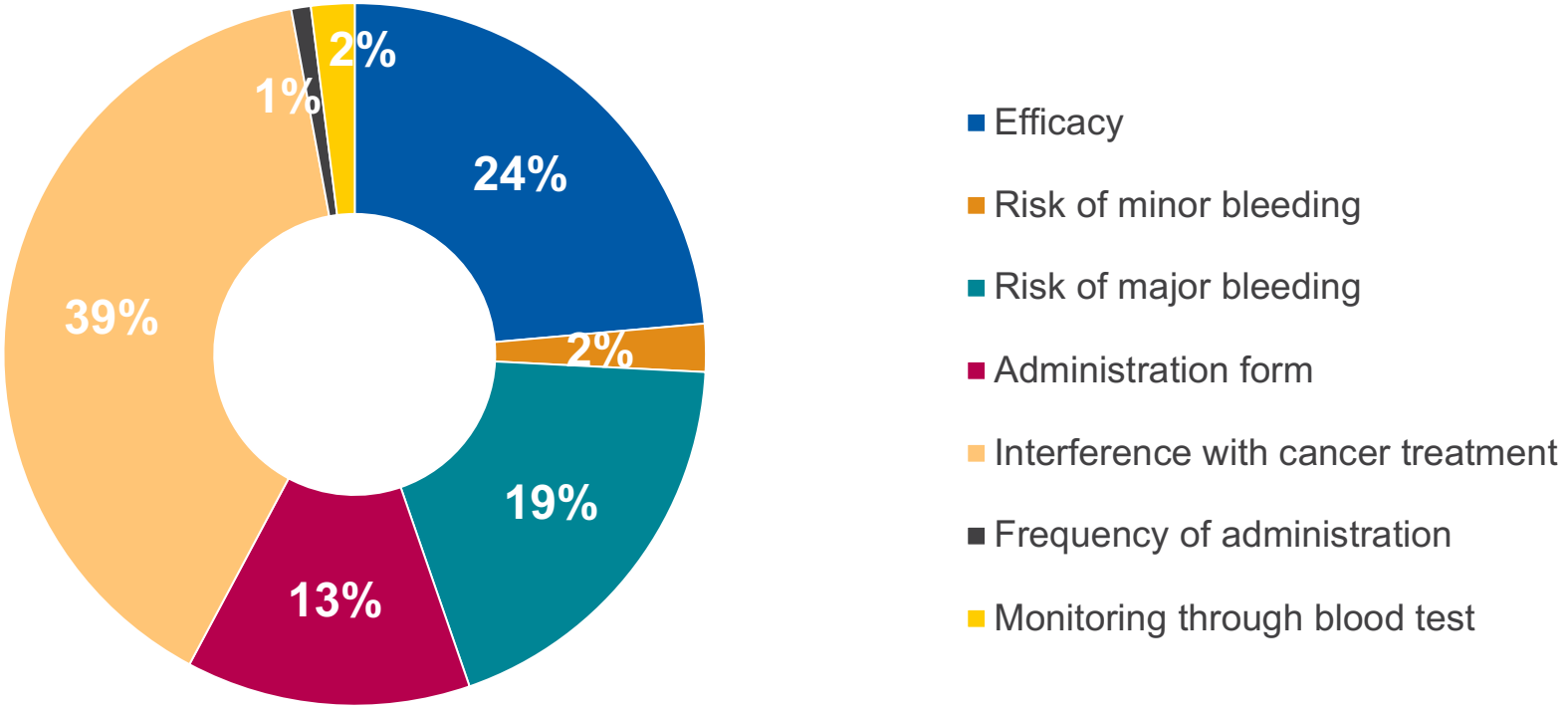

* Significant difference to Germany

Care and support through terminal illness

Marie Curie

# Interference with cancer treatment is the most important attribute to patients, followed by efficacy of VTE therapy

## Relative importance of attributes* - Total




*n = 100*

* Impact / weight of each attribute on the overall preference / choice behavior

Care and support through terminal illness

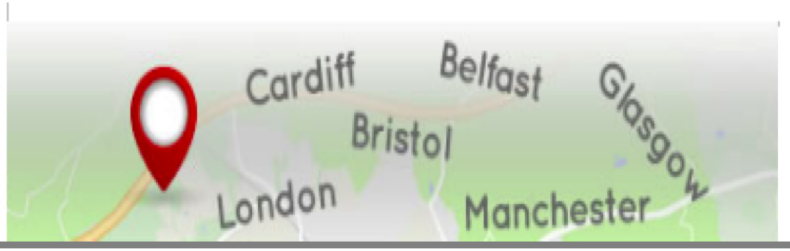
Marie Curie

# To conclude

1. DOACs non inferior to LMWH for CAT
2. Better in preventing VTE recurrence
3. Increased bleeding risk (GI/ urothelial)
4. Drug drug interations


Marie
Curie
Care and support
through terminal illness

LET'S TALK CLOTS NATIONAL CONFERENCES

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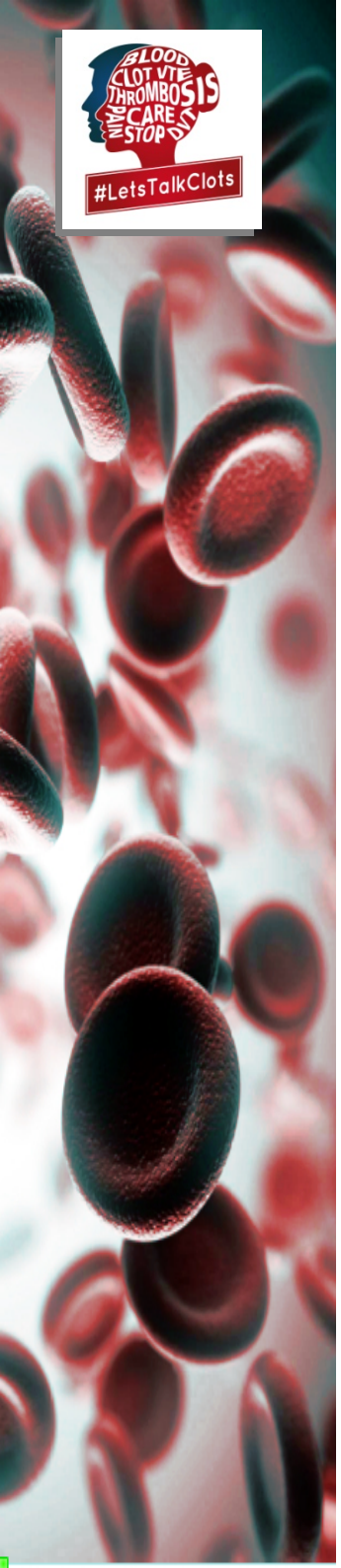
# From NICE cg92 to ng89

*What changes in practice for a Pharmacist on a surgical ward?*




# Learning outcomes

- **Pharmacy team** opportunities of impact on the patient's journey
- Why **thrombosis** is an important area to focus on
- Impact of **NG89** on the activity of our ward
- Impact of our **thrombosis committee** on the VTE rate and patient safety

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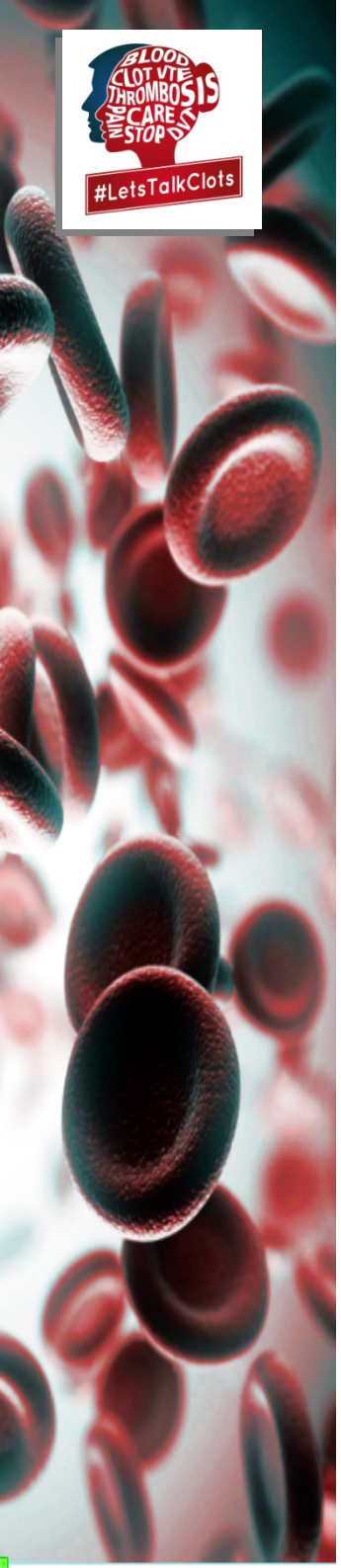
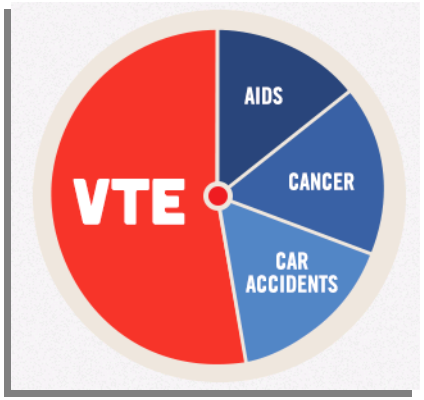



# Pharmacist's role on a ward and why **thrombosis** is a priority?

- **Opportunities for intervention:**
  - Clinical screening of prescriptions
  - Medicine reconciliation
  - Ward round with the MDT/solo
  - Discharge medication




- **Thrombosis** is the 1st preventable cause of death at hospital

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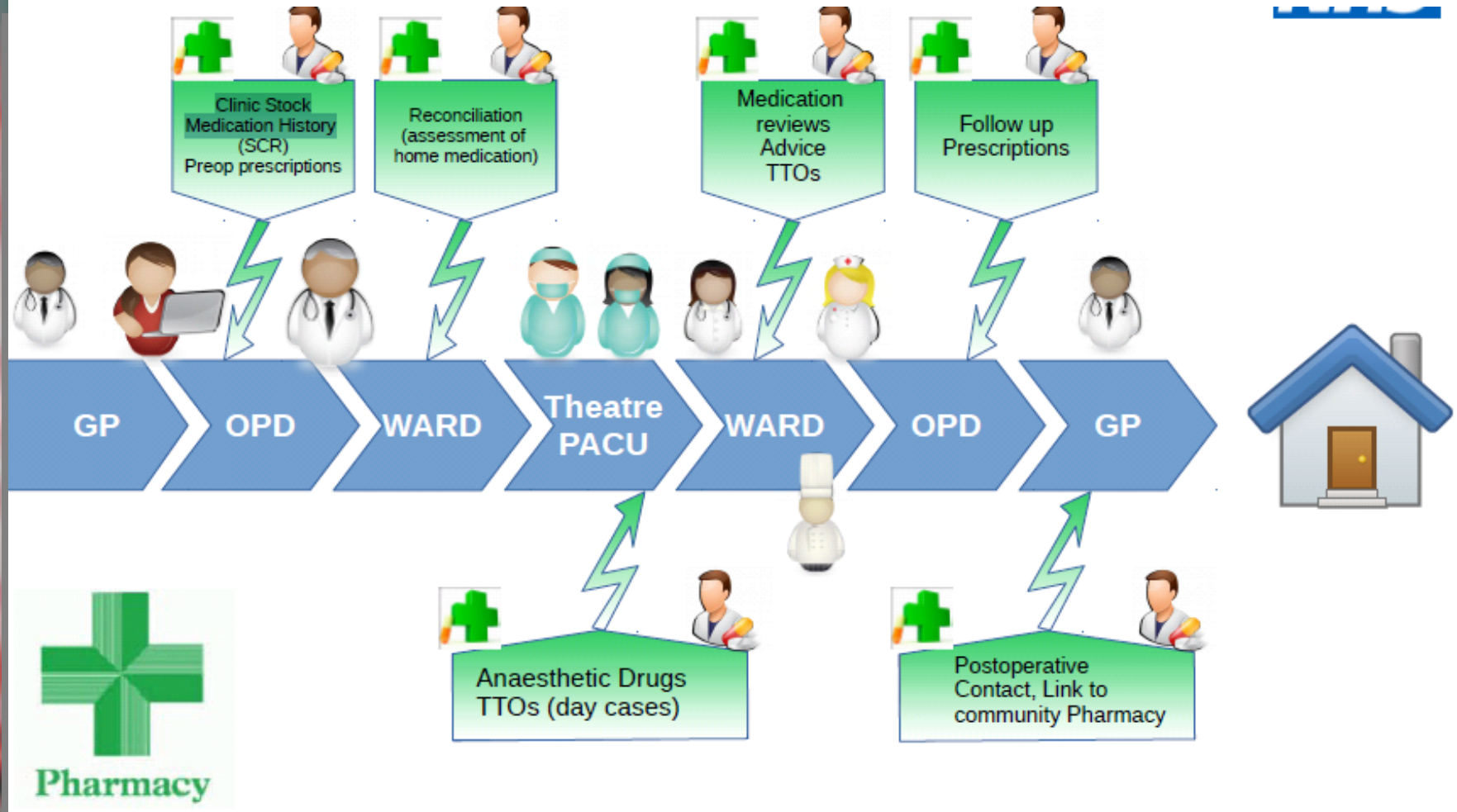
# Opportunities for Pharmacy teams to have an impact on **thrombosis**

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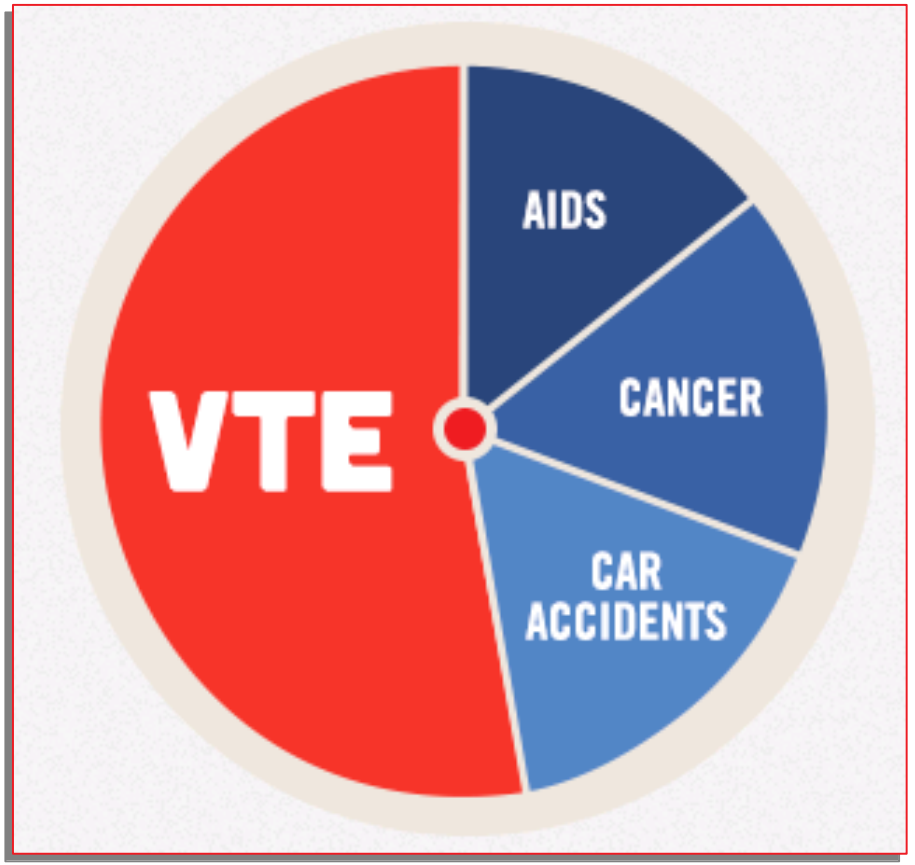
# Why I chose **thrombosis** as a priority?




**Up to 60%**
**of all VTEs are hospital-associated**

Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. Thromb Haemost. 2007;98:756-764, ISTH

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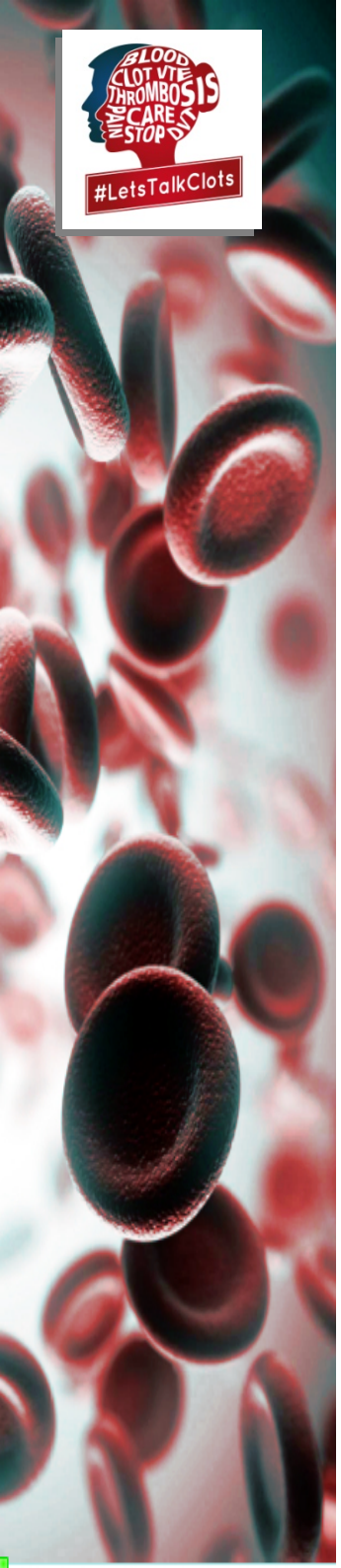
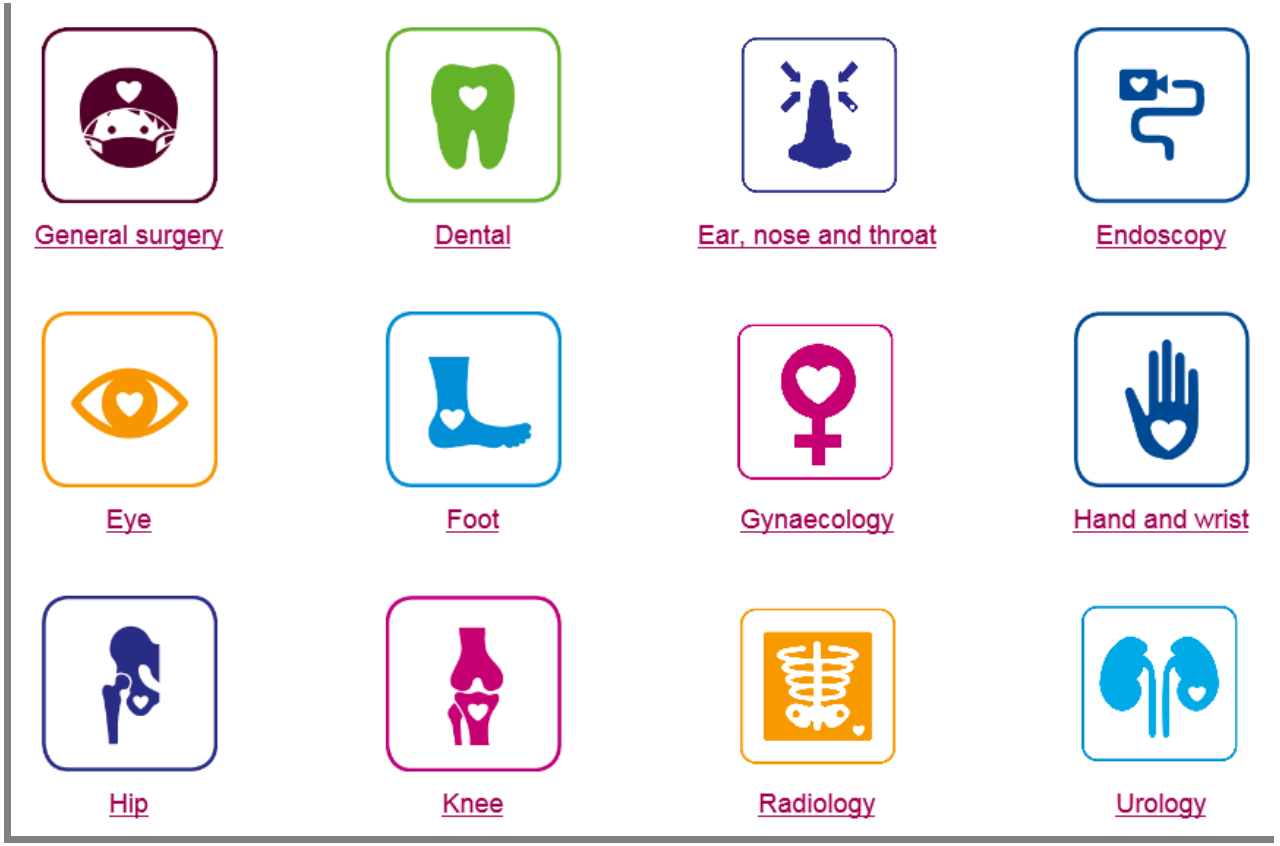



# Our settings and surgical specialities

- 2 Sites: Emersons Green Bristol and Devizes
- Emersons: Day cases and inpatients (33 beds)
- Devizes: Day cases only

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# From NICE CG92 to NG89: timeline

- **2006: APPG** (All Party Parliamentary Group)
- **2010: First NICE guideline CG92**
- **2015: Brief review** (Care-UK HC44)
- **2018: Major review** (indirect Care-UK input)
  - ~~**CG92**~~ renamed **NG89**

Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

NICE guideline
Published: 21 March 2018
nice.org.uk/guidance/ng89

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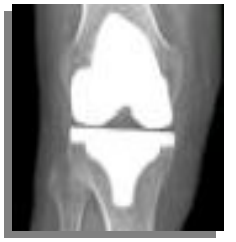
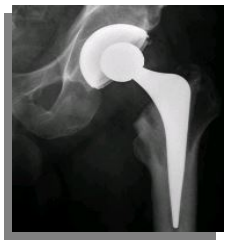
# The impact of NG89 per speciality





**Orthopaedics**

- Elective Total Knee Replacement (TKR)
- Elective Total Hip Replacement (THR)
- Unilateral Knee Replacement and ACL
- Foot and ankle surgery

**Abdominal surgery**

- Gastrointestinal surgery (hernias, Laparoscopic cholecystectomy)
- Gynaecological surgery (major)
- Urology surgery (major )

**ENT**

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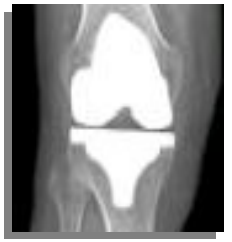
# Total knee arthroplasty

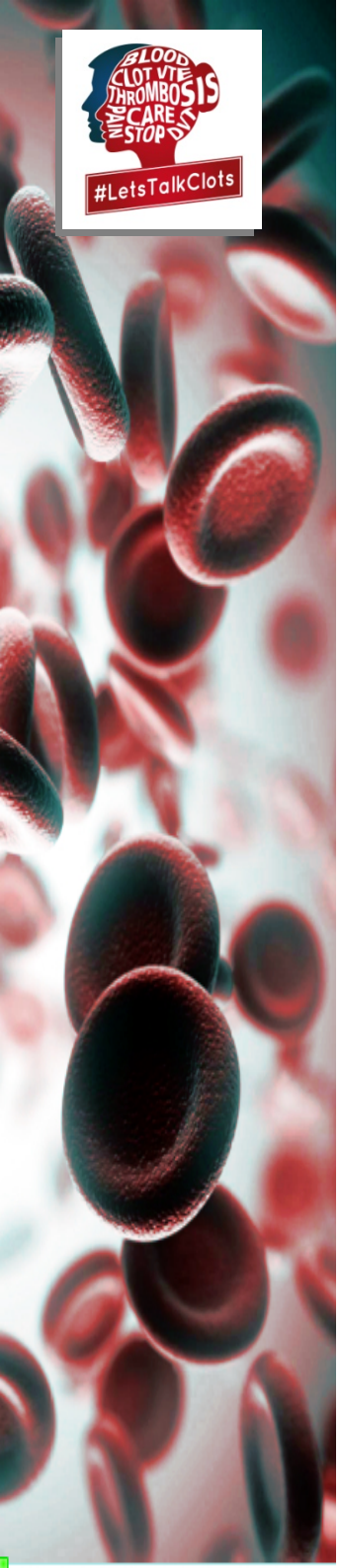


- Choice of **aspirin dose**: 75mg or 150mg?
- Which patient suitable for which agent?
- How can the Pharmacy team support prescribers?

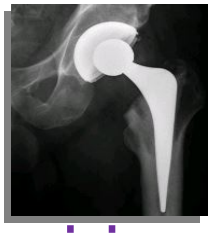
**Elective knee replacement**

1.5.11 Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding. Choose any one of:

- aspirin[7] (75 or 150 mg) for 14 days.
- LMWH[5] for 14 days combined with anti-embolism stockings until discharge.
- Rivaroxaban[8], within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] **[2018]**




# HIP arthroplasty



- Hybrid course with patient home with aspirin and clexane -> potential risk
- Total duration 38 days -> unusual duration

**Elective hip replacement**

1.5.8 Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding. Choose any one of:

- LMWH[5] for 10 days followed by aspirin[7] (75 or 150 mg) for a further 28 days.
- LMWH[5] for 28 days combined with anti-embolism stockings (until discharge).
- Rivaroxaban[8], within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] **[2018]**

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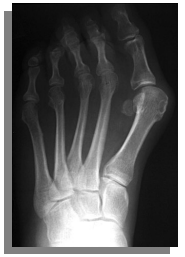
# Foot and ankle surgery



- Importance of assessment
- Balance the risk of VTE vs. risk of bleeding
- Consider local population
  - Our retrospective: 2 VTE were foot surgery

## Foot and ankle orthopaedic surgery

1.5.17 Consider pharmacological VTE prophylaxis for people undergoing foot or ankle surgery:

- that requires immobilisation (for example, arthrodesis or arthroplasty); consider stopping prophylaxis if immobilisation continues beyond 42 days (see recommendation 1.5.4) **or**
- when total anaesthesia time is more than 90 minutes **or**
- the person's risk of VTE outweighs their risk of bleeding. **[2018]**

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# Abdominal surgery

- "Intermediate" risk surgery -> 7 days of LMWH
  - No more single shot of LMWH…

**Abdominal surgery**

1.5.37 Offer VTE prophylaxis to people undergoing abdominal (gastrointestinal, gynaecological, urological) surgery who are at increased risk of VTE. For people undergoing bariatric surgery, follow recommendations 1.5.41–1.5.43. **[2018]**

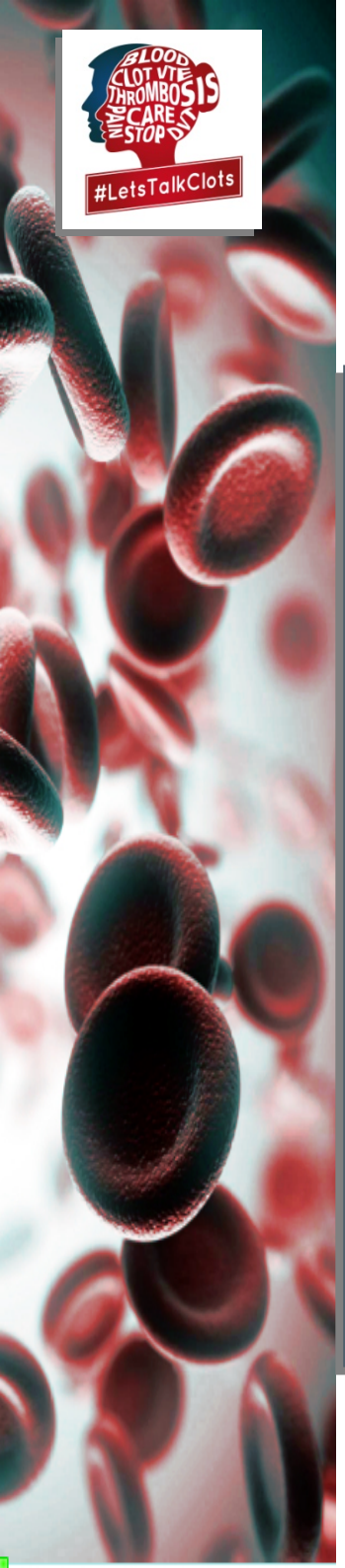
1.5.38 Start mechanical VTE prophylaxis on admission for people undergoing abdominal surgery. Choose either:

- anti-embolism stockings **or**
- intermittent pneumatic compression.

Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. **[2018]**

1.5.39 Add pharmacological VTE prophylaxis for a minimum of 7 days for people undergoing abdominal surgery whose risk of VTE outweighs their risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose either:

- LMWH[s] **or**
- fondaparinux sodium[s]. **[2018]**



# Some important additions/precisions

**Hydrate and keep mobile**

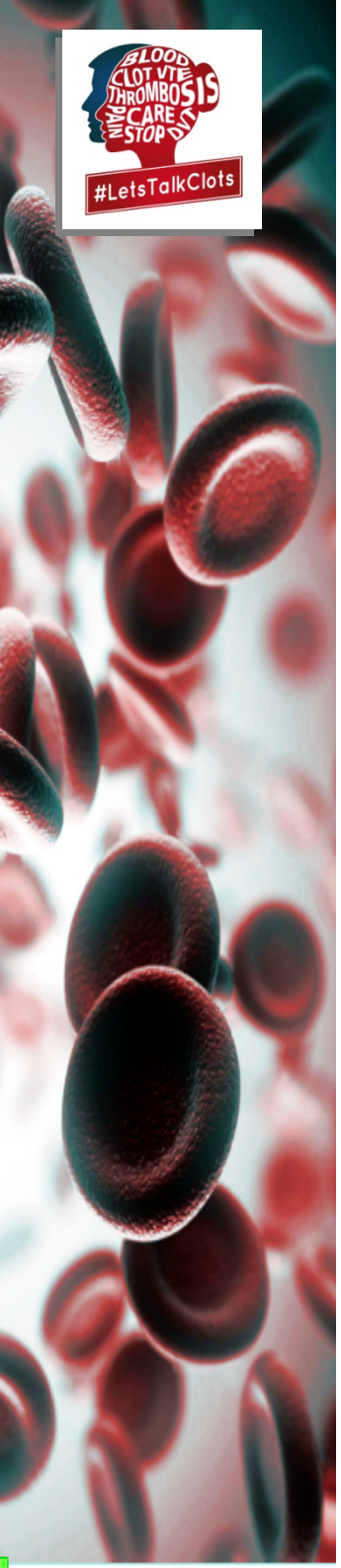
- how people can reduce their risk of VTE (such as keeping well hydrated and, if possible, exercising and becoming more mobile). [2018]

**Signs of VTE**

- the importance of seeking help if DVT, pulmonary embolism or other adverse events are suspected. [2018]

**Safety net**

- the importance of seeking help and who to contact if people have problems using VTE prophylaxis. **[2018]**




# To date: Outcomes following our thrombosis committee's action

- **Monthly communication at Clinical Governance meetings**
- **Direct input in CareUK national guidance**
- **Creation of flowcharts to simplify our national VTE policy**
- **Re-design of our VTE electronic assessment**
- **Significant reduction of VTE event** ($X^2$, IC 95%)

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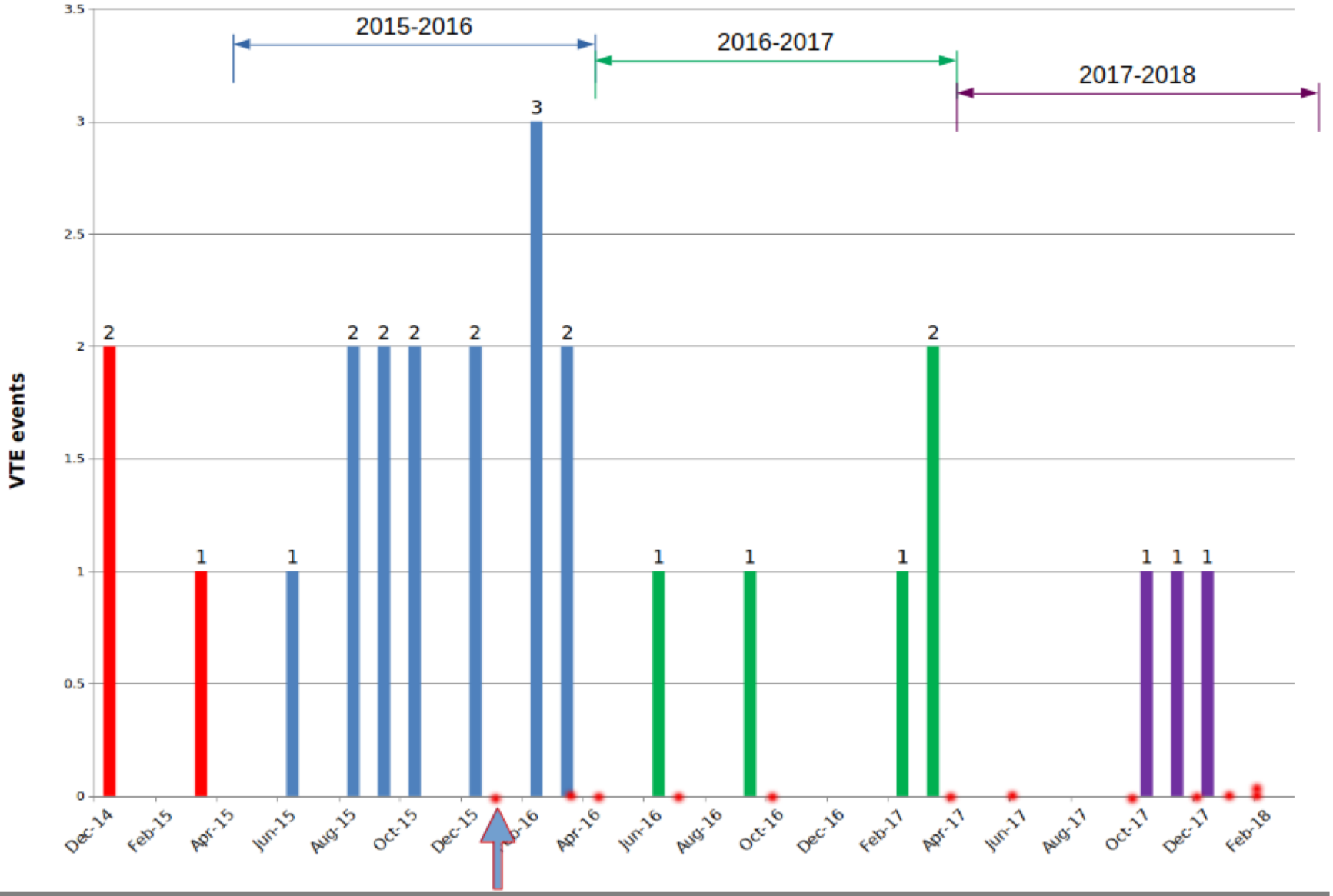
# Results so far of our thrombosis committee's action

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# Where we would like to be next (VTE excellence etc...)

- **Follow North Bristol Trust (NBT) into gaining recognition:**
- **VTE exemplar centres**


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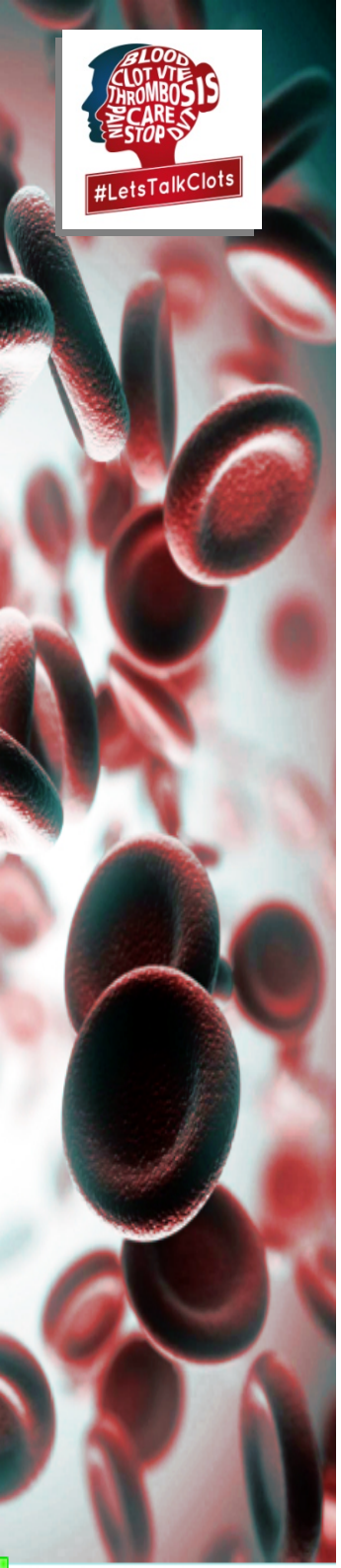


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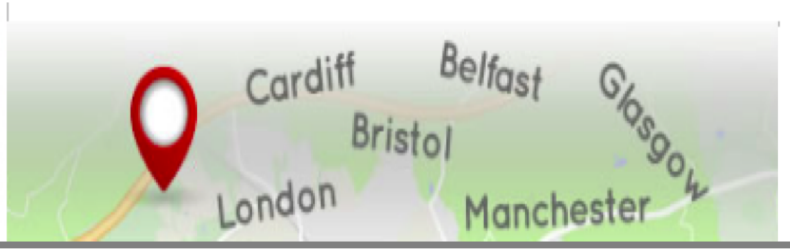
# LET'S TALK CLOTS NATIONAL CONFERENCES

#LetsTalkClots

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Thrombosis Committee (since 2016)

@sjaglin

Team Pharma!

# Practical tips in initiating and maintaining anticoagulation

Sue Bacon

Lead Anticoagulation and VTE prevention Nurse at NBT

# Questions to ask:

- What is the diagnosis?
- Which anticoagulant?
- How to choose?
- How to initiate?
- How to switch between anticoagulants
- Follow up?

# Diagnosis requiring anticoagulation

Prevention of stroke in Atrial Fibrillation (AF)

Treatment of venous thromboembolism

Replacement heart valves, bioprosthetic and mechanical

Arterial Embolus

Arterial disease

Cardiac problems

and many others

# Which anticoagulant?

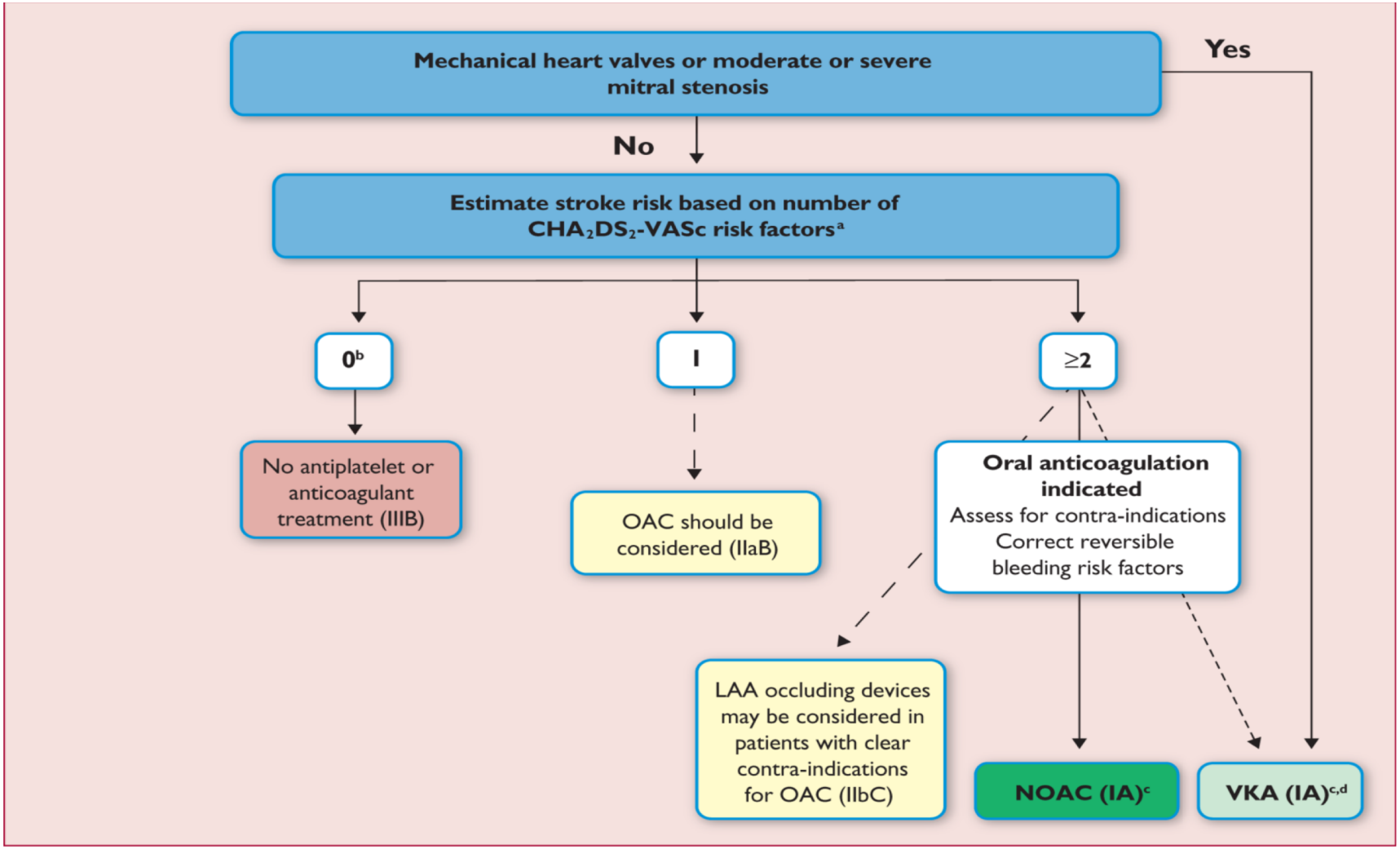
- Vitamin K antagonists
  - Warfarin, sinthrome, acenocoumarol, phenindione
- Non Vit K antagonists (NOACs)
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- LMWH (including fondaparinux)

# How to choose in VTE?

- Traditionally LMWH and then initiation with warfarin, continuing with LMWH for 5/7 *and* until INR >2.0 for 2 days
- LMWH only if active malignancy
- Now – NOACs most likely to be used as first line treatment

| Drug | Initial Treatment | Continued |
|---|---|---|
| Dabigatran | LMWH 5/7 | 150mg twice daily |
| Rivaroxaban | 15mg BD 21 days | 20mg OD<br>(10mg od if equipoise) |
| Apixaban | 10mg BD 7/7 | **5 mg BD for 6 months [2.5 mg BD if equipoise]** |
| Edoxaban | LMWH 5/7 | 60 mg once daily<br>**(30mg OD reduced dose depending on risk factors)** |

# How to choose in AF? (ESC guidance)




AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor.
[d]IB for patients with mechanical heart valves or mitral stenosis.

# Initiation of Warfarin for VTE

- Decide on initiation dose (in hospital use the warfarin chart for guidance)
- Consider the age of the patient ( e.g.. Elderly and frail needs less warfarin as compare to young patient)
- Ensure adequate warfarin counselling – involve family member
- Try to give consistent doses
- In hospital - Daily INR's only required on Day 1-4, and following dosing tables on the warfarin chart
- Have they been on warfarin before – what dose did they take
- What other drugs are they taking? (HIV and rifampacin reduce the INR whereas medication - amiodarone may increase the INR)
- When INR >2.0 do not dose reduce but continue until INR nearly 2.5 and then stop LMWH

# Initiation of warfarin for AF

- As for VTE – but cover with LMWH not required (although mentioned in NICE update 2014 – only for symptomatic patients in hospital)
- Start on 5mg – standard, INR on day 5 and 8
- Frail and elderly (or those who had low dose previously) 2mg/3mg –if frail and also on interacting drugs - ?amiodarone
- Dosing by following TAIT – adjust if not starting on 5mg

# NOACs and AF

| Drug | Action | Dose | ½ life hours | Excretion | Routine tests req pre initiation | Storage | Food |
|---|---|---|---|---|---|---|---|
| Rivaroxaban<br><br>ROCKET-AF | Activated FXa | 20mg od<br>15mg od | 5-9<br>11-13 | 35% renal<br>65% liver | none | No probs | Plus 39% |
| Dabigatran<br><br>RELY | Thrombin | 150mg bd<br>110mg bd | 12-17 | 80% renal<br>20% liver | U&E then yearly | In airtight container | none |
| Apixaban<br><br>ARISTOTLE AVERROES | Activated FXa | 5mg bd<br>2.5mg bd | 12 | 27%renal<br>73% liver | LFT | No probs | none |
| Edoxaban<br><br>ENGAGE-AF | Activated FXa | 60mg od<br>30mg od<br>15mg od | 9-11 | 50% renal<br>50% liver | | No probs | Plus 6-22% |

# Choosing the correct dose

- NOACs provide simple dosing  True/False?
- No monitoring required  True/False
- NOACs in obese patients? – what is the top limit of weight?
- No drug interactions?

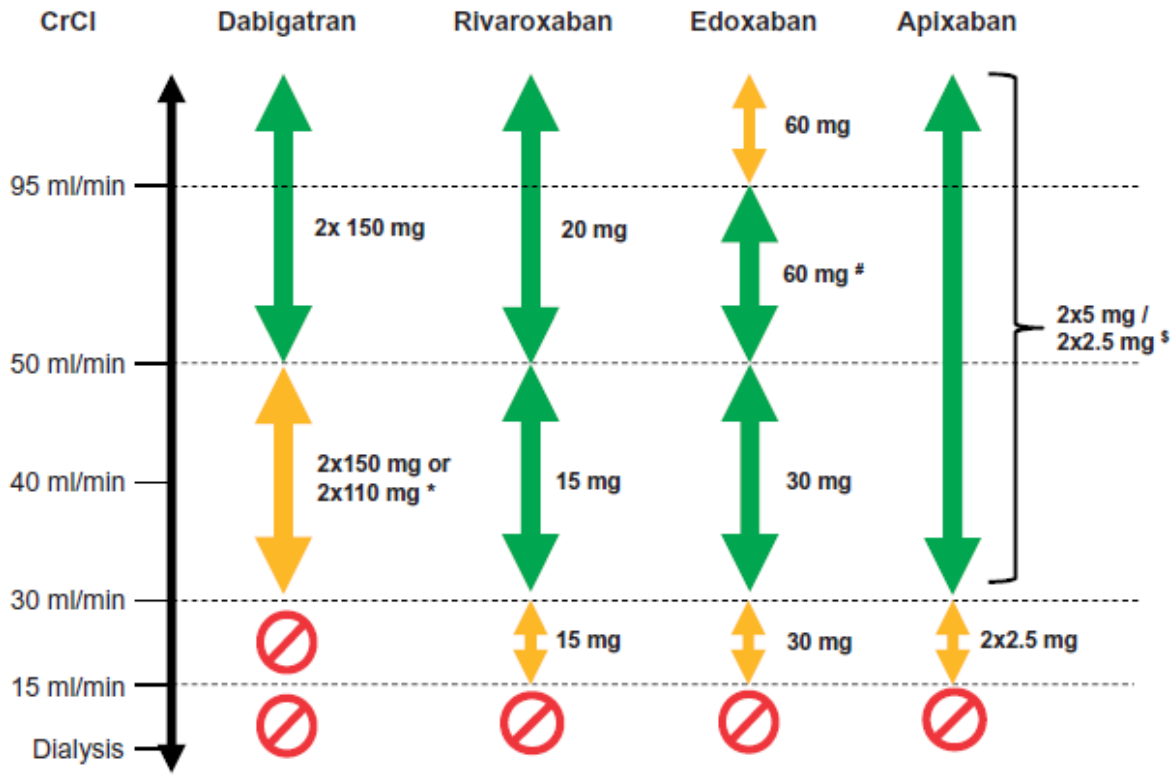



**Figure 4** Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

# Maintaining anticoagulation: Warfarin

- Ensure that Drs are aware when a patient is not eating as this may affect the INR
- INRs are taken more frequently when new drugs added or patient deteriorates
- Interacting drugs should be noted ( ie antibiotics & vitamin K – when prescribing antibiotics check INR at that point as if unwell INR likely to be elevated)
- In hospital - ensure that box 4 is completed (patients normal warfarin dose) for patients admitted on warfarin to ensure safe re-anticoagulation post surgery etc
- On discharge - Patients need to know the date and time for first INR post discharge – write it down.

# Maintaining Anticoagulation: Warfarin

- Regular INRs tests
- Not too often – a small dose change may take 2 weeks to affect the INR
- When patients unwell – take an INR then, before starting the antibiotics
- Advise patient to get INR done if they begin to feel unwell – not to wait till next INR
- Switch to NOACs:-
  - If TTR <65%
  - Why is TTR poor – if non compliance stay with warfarin unless eg dosset box
  - If the INR fluctuates – Variance Growth Rate (VGR) – predictive of an event
  - Unable to get to surgery for INR and require a DN
  - INR >8 x1
  - Having too many INR tests
  - Patient choice

# What is included in follow up?

| | When | How |
|---|---|---|
| Adherence | Each visit | Discussion<br>Reinforce importance<br>Discuss adherence aids (my therapy – dosset box) |
| Thromboembolism | Each visit | Any events? |
| Bleeding | Each visit | Nuisance bleeding<br>Bleeding impacting on QoL |
| Assessing modifiable risk factors for bleeding | Each visit | Eg – hypertension, meds that increase bleeding – aspirin, labile INR, alcohol |
| Co-medications | Each visit | Over the counter drugs |
| Hb, U&E, LFT | Yearly<br>6 monthly<br>As needed | Mainly looking at renal function |
| Check correct dose and NOAC | Each visit | Reassess that the chosen anticoagulant is<br>a) The best for the patient<br>b) The dose is correct |

# Switching

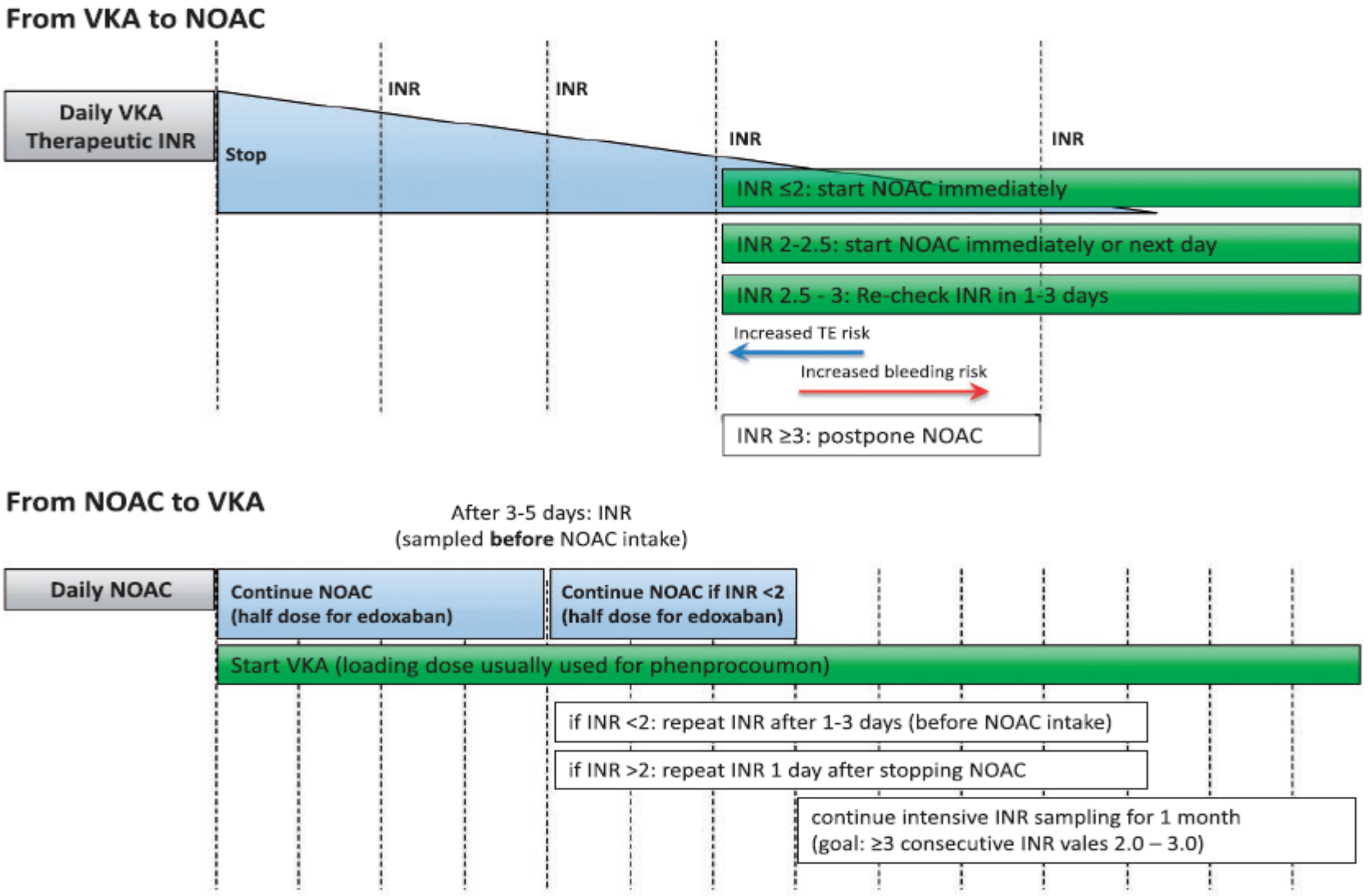



**Figure 2** Switching between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants and vice versa. TE, thromboembolic.