VTE Exemplar Centres
Providing leadership in thrombosis care

Oxford University Hospitals NHS
NHS Foundation Trust

# Review of the evidence to support pharmacological thromboprophylaxis in medical and surgical patients

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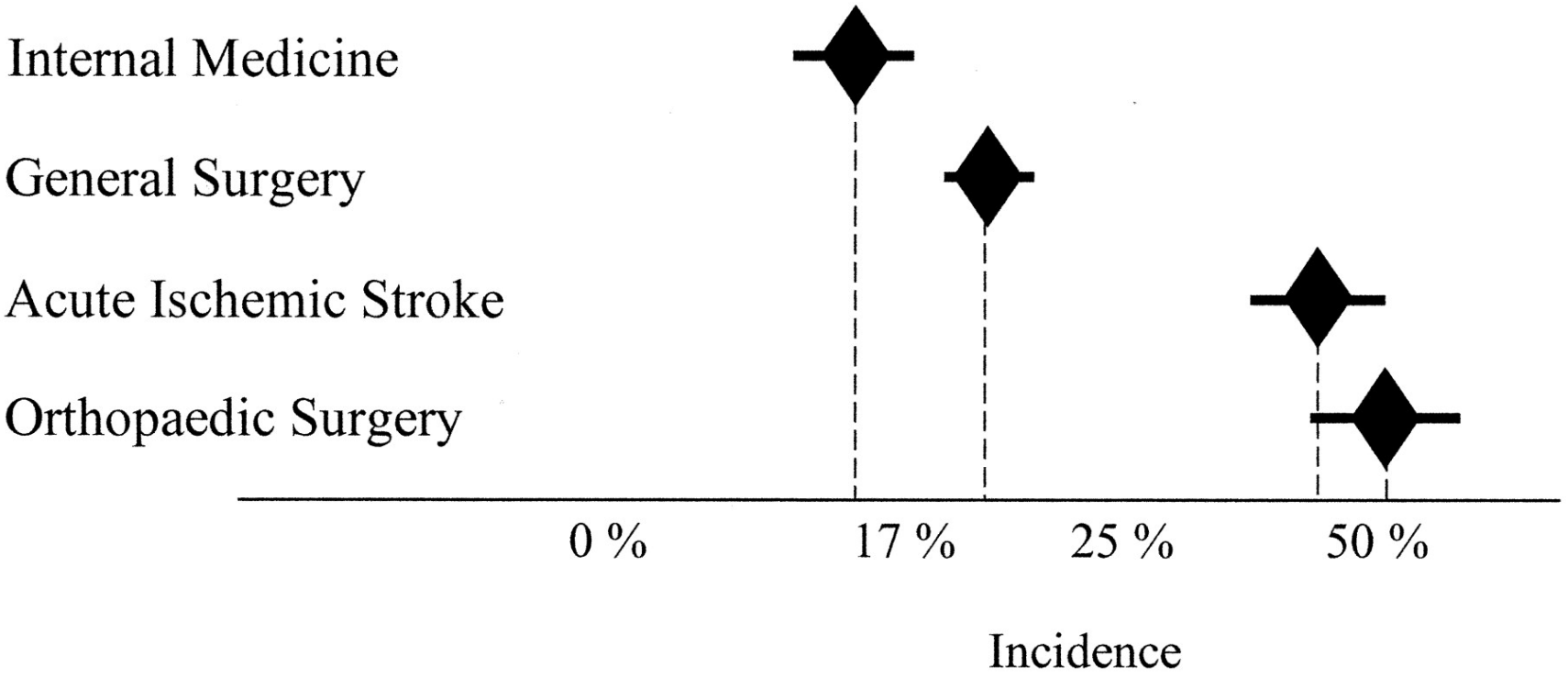
# Evidence

- VTE risk associated with hospitalisation
- Strategies to reduce this risk
- Gaps in the evidence

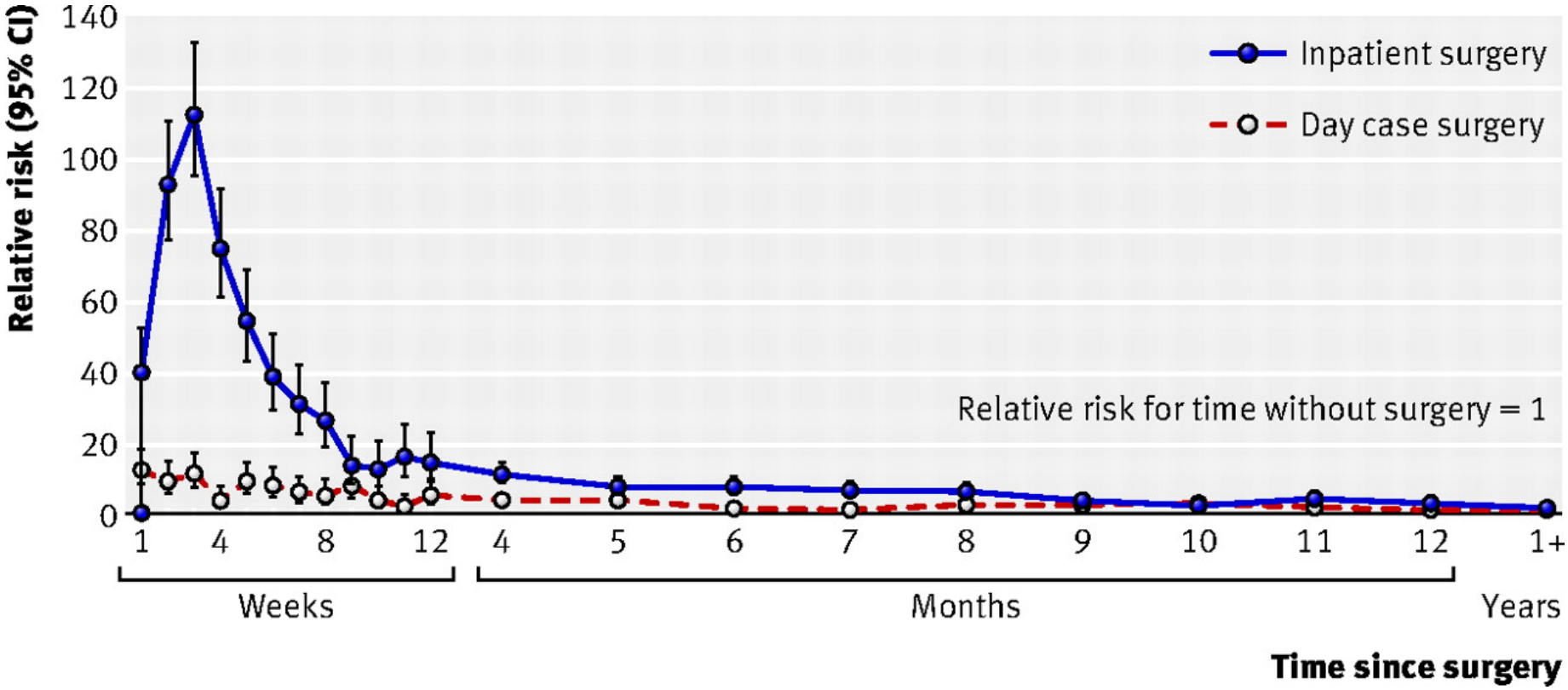
# Risk of DVT as inpatient without prophylaxis




American Heart Association.

Alain Leizorovicz, and Patrick Mismetti Circulation. 2004;110:IV-13-IV-19

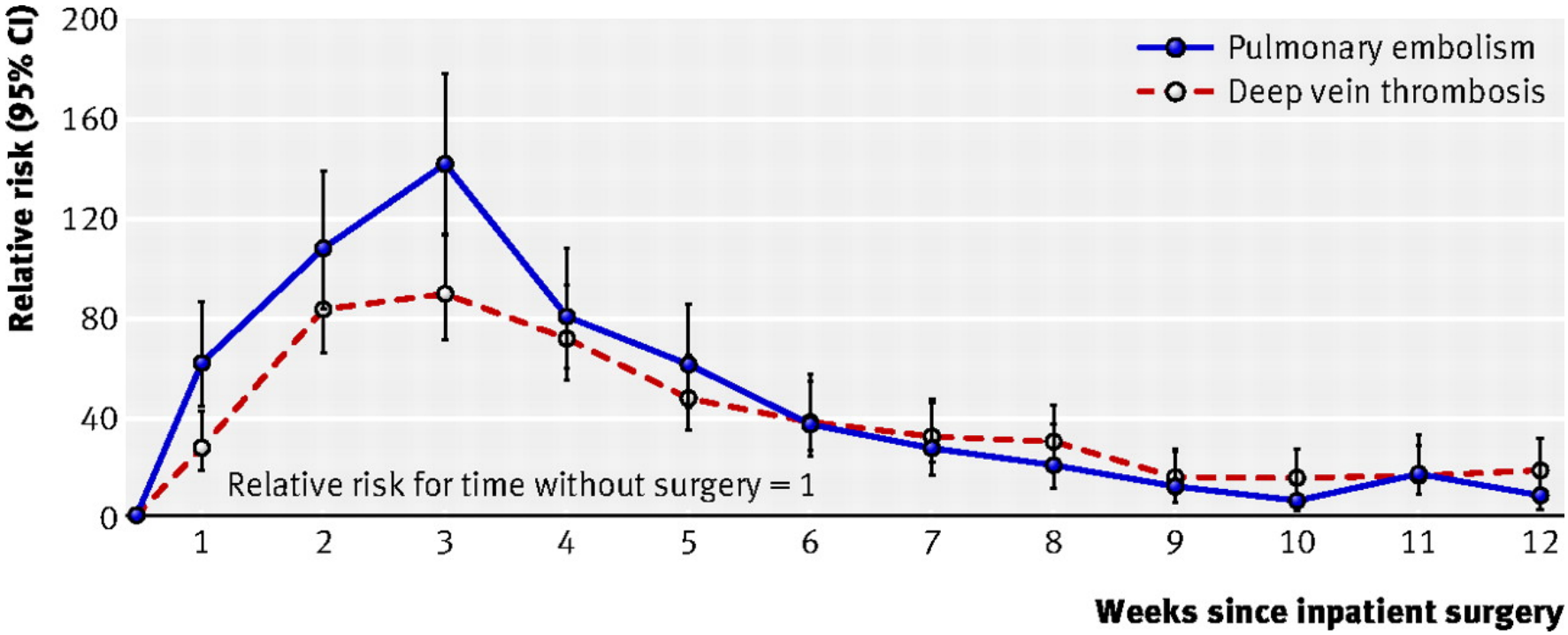
# Relative risk of VTE by time since surgery




thebmj

Siân Sweetland et al. BMJ 2009;339:bmj.b4583

# Relative risks of PE and DVT by time since inpatient surgery

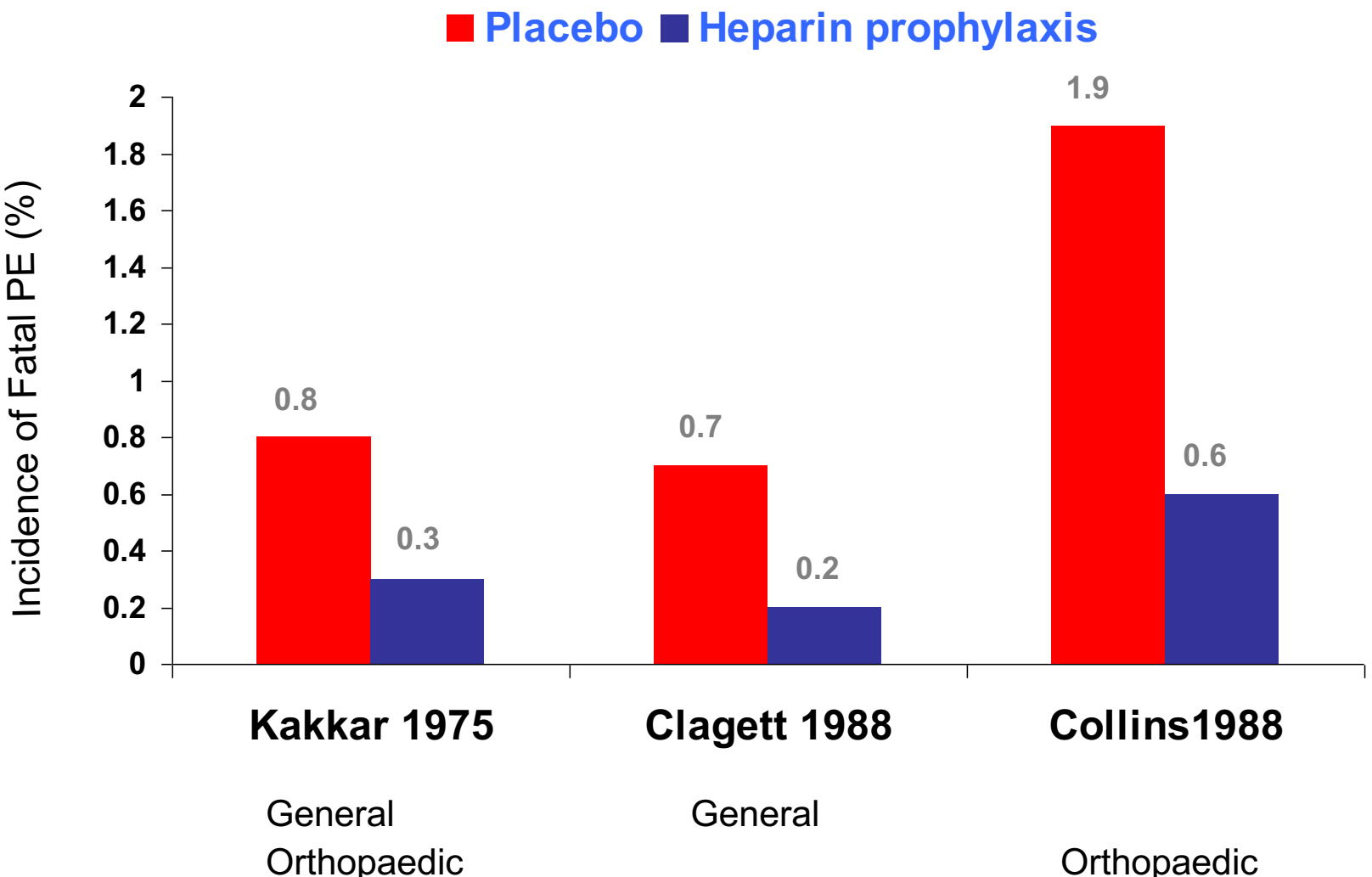



thebmj

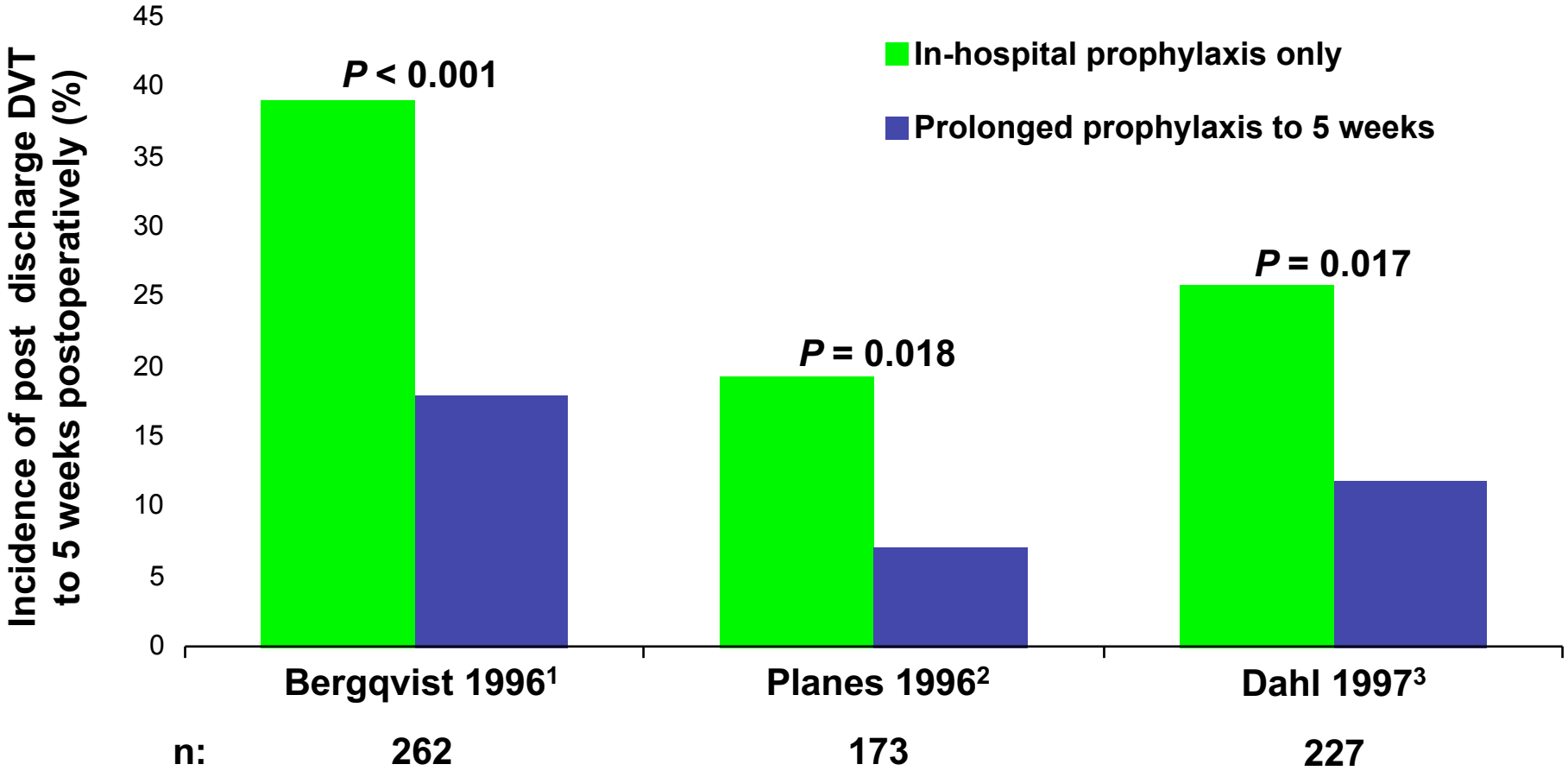
Siân Sweetland et al. BMJ 2009;339:bmj.b4583

# Surgical patients

# Reduced rate fatal PE post surgery with heparin thromboprophylaxis



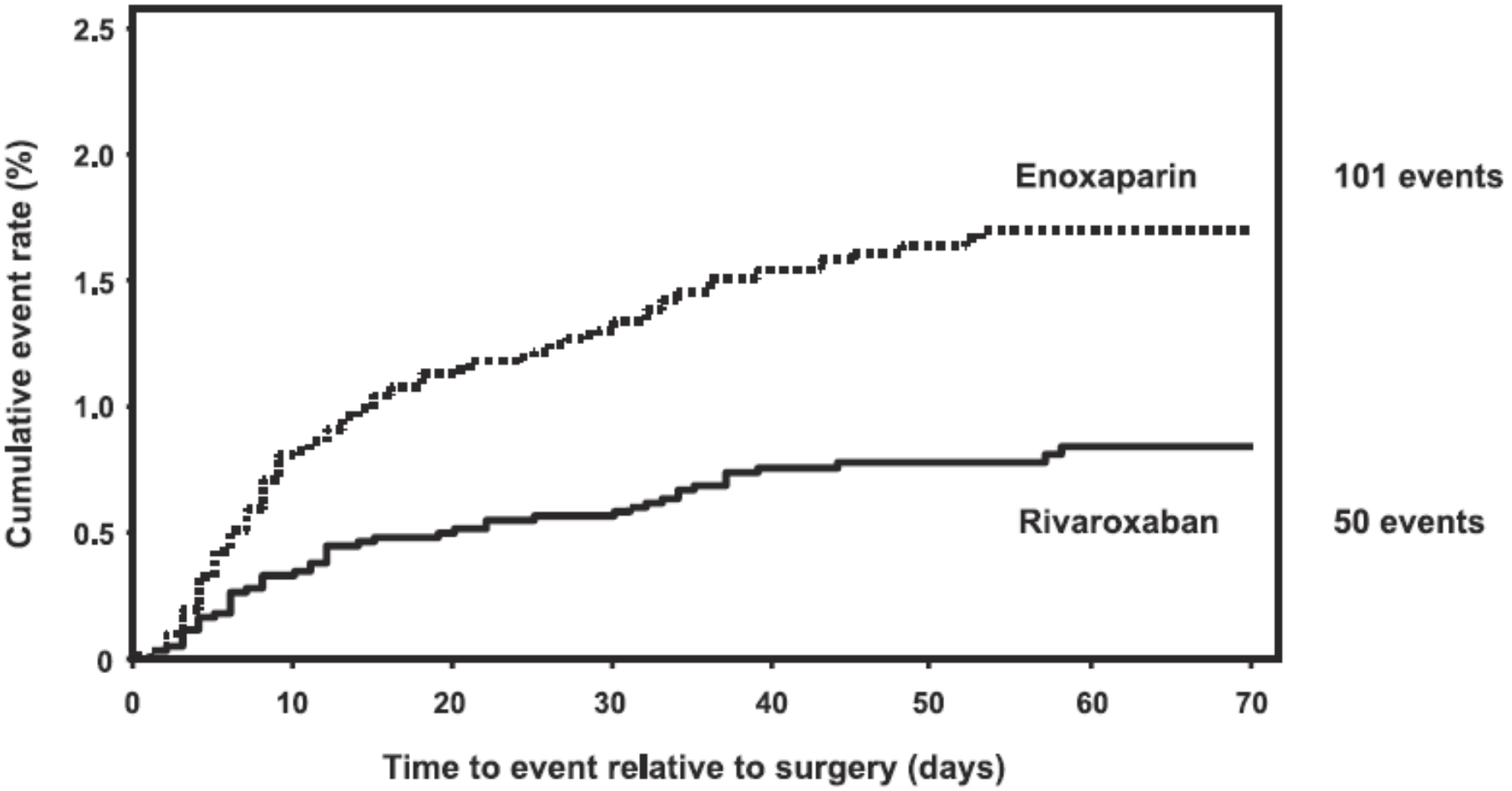
# Evidence for extended LMWH prophylaxis post surgery (THR)




Adapted from Agnelli G et al. *Blood Coagul Fibrinolysis*. 1999;10(suppl 2):S29-S35. [1]Bergqvist D et al. *N Engl J Med*. 1996;335:696-700. [2]Planes et al. *Lancet*. 1996;348:224-8. [3]Dahl OE et al. *Thromb Haemost*. 1997;77:26-31.

# RECORD 1-4, Pooled Data, Rivaroxaban THR and TKR

## Symptomatic VTE and all cause mortality




Turpie et al 2011 Thromb Haemost 2011; 105: 444–453

# RECORD 1-4, Pooled Data, Rivaroxaban THR and TKR

| | **Symptomatic VTE and all cause mortality** | **Major bleeding** | **MB and CRNMB** |
|---|---|---|---|
| Enoxaparin 40mg (or 30mg bd) | 1% | 0.2% | 2.5% |
| Rivaroxaban 10mg | 0.5%<br>P=0.001 | 0.3%<br>P=0.023 | 2.8%<br>P=0.19 |

Turpie et al 2011 Thromb Haemost 2011; 105: 444–453

# EPCAT 1

- RCT, non-inferiority design
- 778 patients, unilateral THR
- 10 days dalteparin then randomised to 28 days dalteparin or aspirin 100mg

| | **Symptomatic VTE** | **MB and CRNMB** |
|---|---|---|
| 10 days dalteparin +28 days aspirin | 0.3%<br>Non-inferior | 0.5%<br>Non-inferior |
| 38 days dalteparin | 1.3% | 1.3% |

Anderson et al 2013, Ann Intern Med 158:800

# EPCAT 2

- RCT, 3396 patients (1804 THR, 1620 TKR)
- THR: 5 days rivaroxaban 10mg then 30 days either rivaroxaban or aspirin 81mg
- TKR: 5 days rivaroxaban 10mg then 9 days either rivaroxaban or aspirin 81mg

| | **Symptomatic VTE** | **MB** | **MB and CRNMB** |
|---|---|---|---|
| Rivaroxaban + aspirin | 0.64%<br>Non-inferior | 0.47% | 1.29% |
| Rivaroxaban | 0.70% | 0.29% | 0.99% |

Weitz et al 2018, NEJM 376:1211

# Aspirin alone TKR – NICE 2018

## NICE network metaanalysis, rank order of interventions

Figure 834: Rank order for interventions based on the relative risk of experiencing DVT

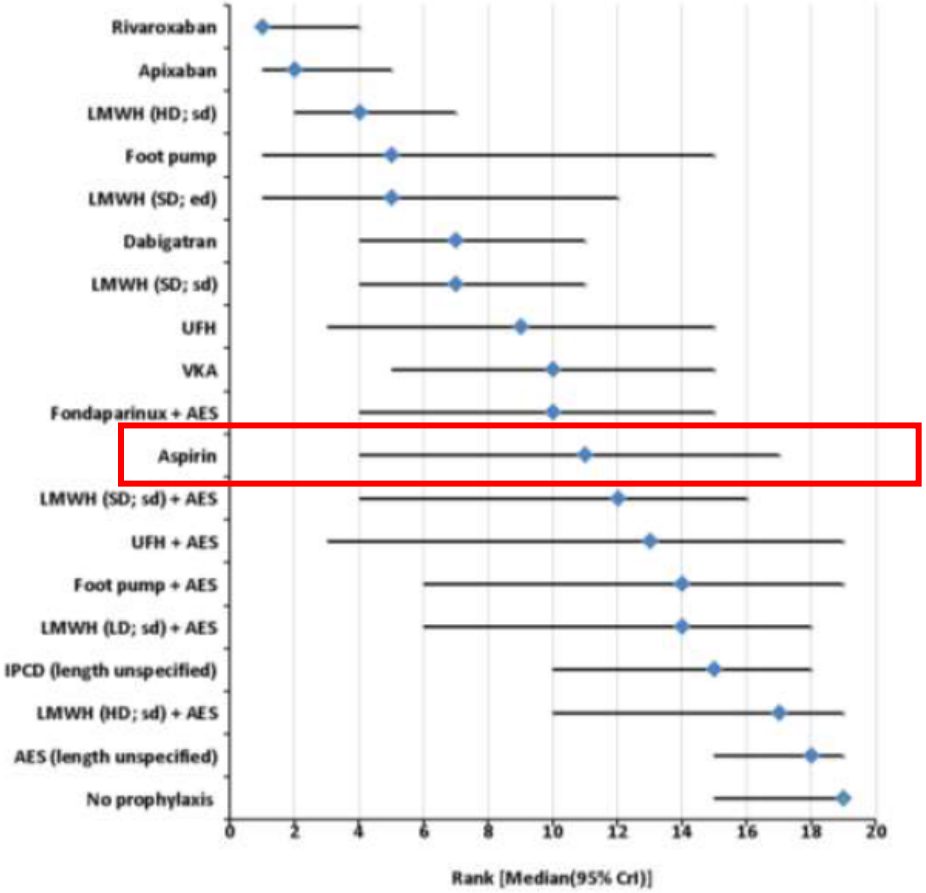



Figure 836: Rank order for interventions based the relative risk of experiencing PE

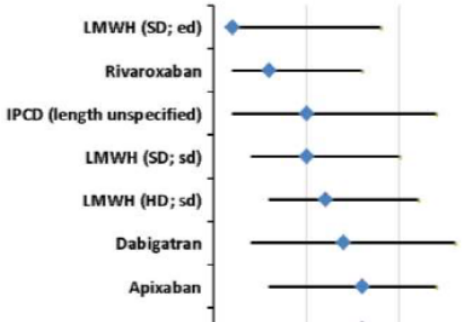
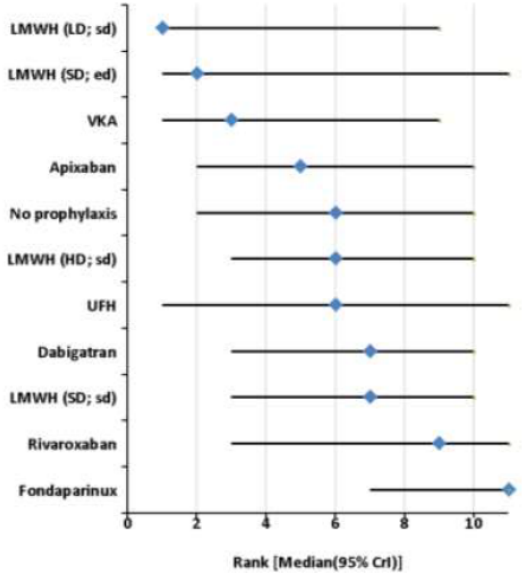



Figure 838: Rank order for interventions based on the relative risk of experiencing major bleeding




Section 27.6 for TKR: "The inclusion of aspirin … was primarily based on the results from the **economic model**

NICE CG89 2018

# Medical inpatients

# LMWH prophylaxis in medical patients

| Study | RRR | Thromboprophylaxis | Patients with VTE (%) |
|---|---|---|---|
| MEDENOX[1] | **63%** | Placebo | 14.9 |
| *P*<0.001 | | Enoxaparin 40 mg | 5.5 |
| PREVENT[2] | **49%** | Placebo | 5.0 |
| *P*=0.0015 | | Dalteparin 5000IU | 2.8 |

NB PREVENT risk of major bleeding 0.49% dalteparin, 0.16% placebo (p=0.15)

[1]Samama MM *et al. N Engl J Med* 1999;341:793–800
[2]Leizorovicz A *et al. J Circulation* 2004;110:874–9

RRR = relative risk reduction

# Medical population in clinical trials of prophylaxis

- Median LOS about 7 days

- > 40 years
- Congestive heart failure, acute respiratory failure
- *Or* other medical conditions (eg acute infection without septic shock; acute rheumatic disorders, inflammatory bowel disease) PLUS
  - age > 75 yrs
  - cancer
  - previous VTE
  - obesity

# Extended thromboprophylaxis for medical inpatients

- EXCLAIM enoxaparin
- ADOPT apixaban
- MAGELLAN rivaroxaban

- APEX betrixaban

# APEX - betrixaban

- Factor Xa inhibitor
- RCT , 7513 patients
- Eligibility:
  - >75 yrs or > 40 yrs and elevated ddimer
  - Plus acute medical illness (CCF, resp failure, ischaemic stroke) with reduced mobility
  - Plus 1 additional VTE risk factor

| | **VTE* Cohort 1 (elevated ddimer)** | **Overall population** | **Major bleeding (MB)** | **MB or CRNMB** |
|---|---|---|---|---|
| Enoxaparin 40mg 10 +/- 4 days | 8.5% | 7.0% | 0.6% | 1.6% |
| Betrixaban 80mg 35-42 days | 6.9%<br>**RR 0.81**<br>**P=0.054** | 5.3% | 0.7%<br>**RR 1.19**<br>**P=0.55** | 3.1%<br>**RR 1.97**<br>**P<0.001** |

*Symptommatic VTE and asymptommatic proximal DVT

# European Medicines Agency

- March 2018, EMA refused marketing authorisation for betrixaban

- “The main study did not satisfactorily show that benefits outweighed its risk [bleeding]
- The results of the study were not considered reliable because some results of tests for blood clots were not available.”


CAMERON SCOTT


CALL THE DOCTOR
IS A BLOOD CLOT READY TO KILL YOU?
wwa
.ORG

# The NHS England VTE prevention tool

## RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

***All patients should be risk assessed on admission to hospital. Patients should be reassessed within 24 hours of admission and whenever the clinical situation changes.***

### STEP ONE

Assess all patients admitted to hospital for level of mobility (tick one box). All surgical patients, and all medical patients with significantly reduced mobility, should be considered for further risk assessment.

### STEP TWO

Review the patient-related factors shown on the assessment sheet against **thrombosis** risk, ticking each box that applies (more than one box can be ticked).

Any tick for thrombosis risk should prompt thromboprophylaxis according to NICE guidance.

The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate.

### STEP THREE

Review the patient-related factors shown against **bleeding risk** and tick each box that applies (more than one box can be ticked).

Any tick should prompt clinical staff to consider if bleeding risk is sufficient to preclude pharmacological intervention.

Guidance on thromboprophylaxis is available at:

*National Institute for Health and Clinical Excellence (2010) Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92. London: National Institute for Health and Clinical Excellence.*

**http://www.nice.org.uk/guidance/CG92**

This document has been authorised by the Department of Health
Gateway reference no: 10278

Department of Health



Department of Health

## RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

| Mobility – all patients (tick one box) | Tick | | Tick | | Tick |
|---|---|---|---|---|---|
| Surgical patient | | Medical patient expected to have ongoing reduced mobility relative to normal state | | Medical patient NOT expected to have significantly reduced mobility relative to normal state | |
| **Assess for thrombosis and bleeding risk below** | | | | **Risk assessment now complete** | |

| Thrombosis risk | | | |
|---|---|---|---|
| **Patient related** | **Tick** | **Admission related** | **Tick** |
| Active cancer or cancer treatment | | Significantly reduced mobility for 3 days or more | |
| Age > 60 | | Hip or knee replacement | |
| Dehydration | | Hip fracture | |
| Known thrombophilias | | Total anaesthetic + surgical time > 90 minutes | |
| Obesity (BMI >30 kg/m²) | | Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes | |
| One or more significant medical comorbidities (eg heart disease;metabolic,endocrine or respiratory pathologies;acute infectious diseases; inflammatory conditions) | | Acute surgical admission with inflammatory or intra-abdominal condition | |
| Personal history or first-degree relative with a history of VTE | | Critical care admission | |
| Use of hormone replacement therapy | | Surgery with significant reduction in mobility | |
| Use of oestrogen-containing contraceptive therapy | | | |
| Varicose veins with phlebitis | | | |
| Pregnancy or < 6 weeks post partum (see NICE guidance for specific risk factors) | | | |

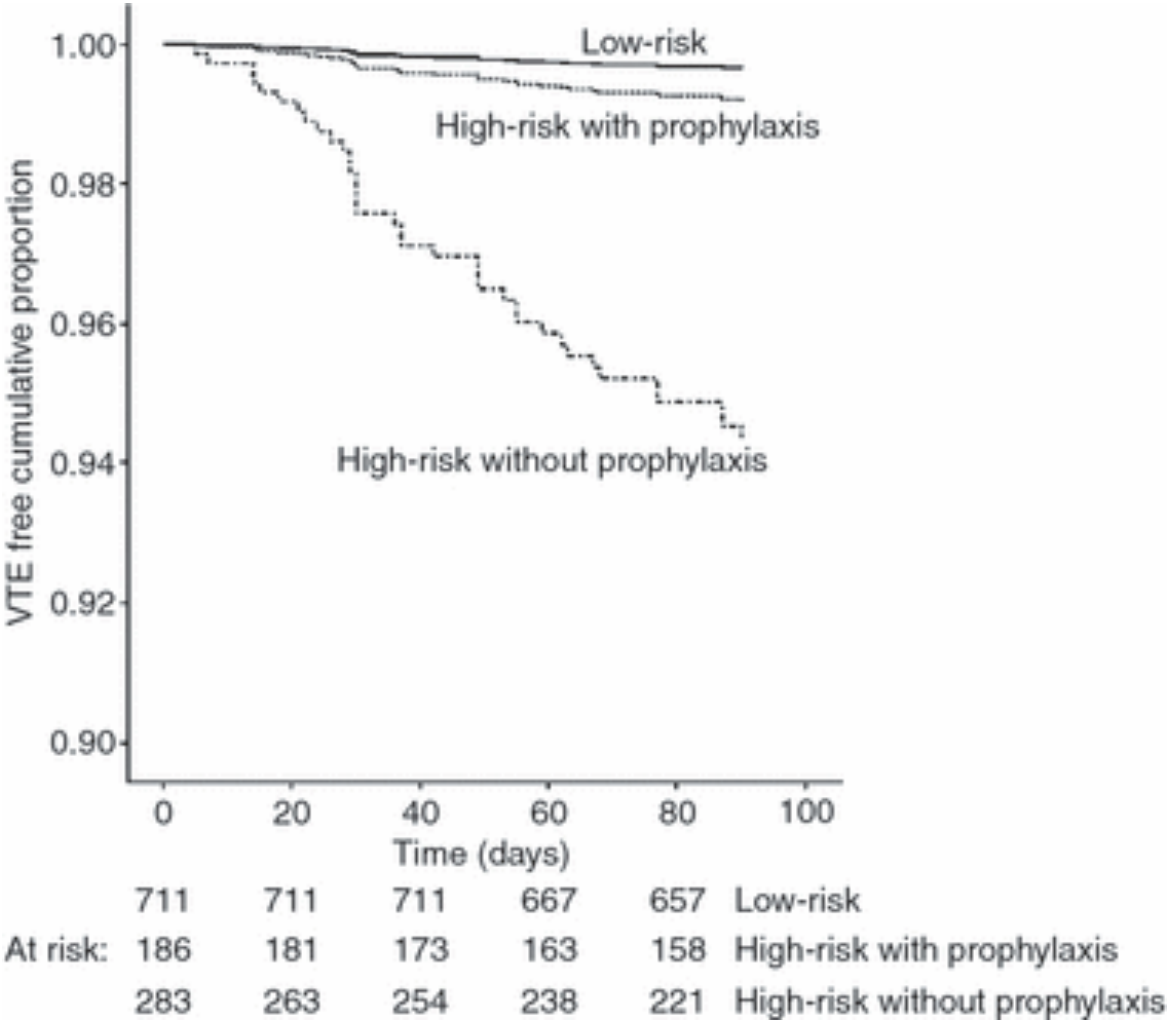
| Bleeding risk | | | |
|---|---|---|---|
| **Patient related** | **Tick** | **Admission related** | **Tick** |
| Active bleeding | | Neurosurgery, spinal surgery or eye surgery | |
| Acquired bleeding disorders (such as acute liver failure) | | Other procedure with high bleeding risk | |
| Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2) | | Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours | |
| Acute stroke | | Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours | |
| Thrombocytopaenia (platelets< 75x10⁹/l) | | | |
| Uncontrolled systolic hypertension (230/120 mmHg or higher) | | | |
| Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease) | | | |

# **Padua Prediction Score,** medical inpatients, high risk 4 or more

| **Baseline features** | **Score** |
|---|---|
| Active cancer* | 3 |
| Previous VTE (with the exclusion of superficial vein thrombosis) | 3 |
| Reduced mobility† | 3 |
| Already known thrombophilic condition‡ | 3 |
| Recent (≤1 month) trauma and/or surgery | 2 |
| Elderly age (≥70 years) | 1 |
| Heart and/or respiratory failure | 1 |
| Acute myocardial infarction or ischemic stroke | 1 |
| Acute infection and/or rheumatologic disorder | 1 |
| Obesity (BMI ≥30) | 1 |
| Ongoing hormonal treatment | 1 |

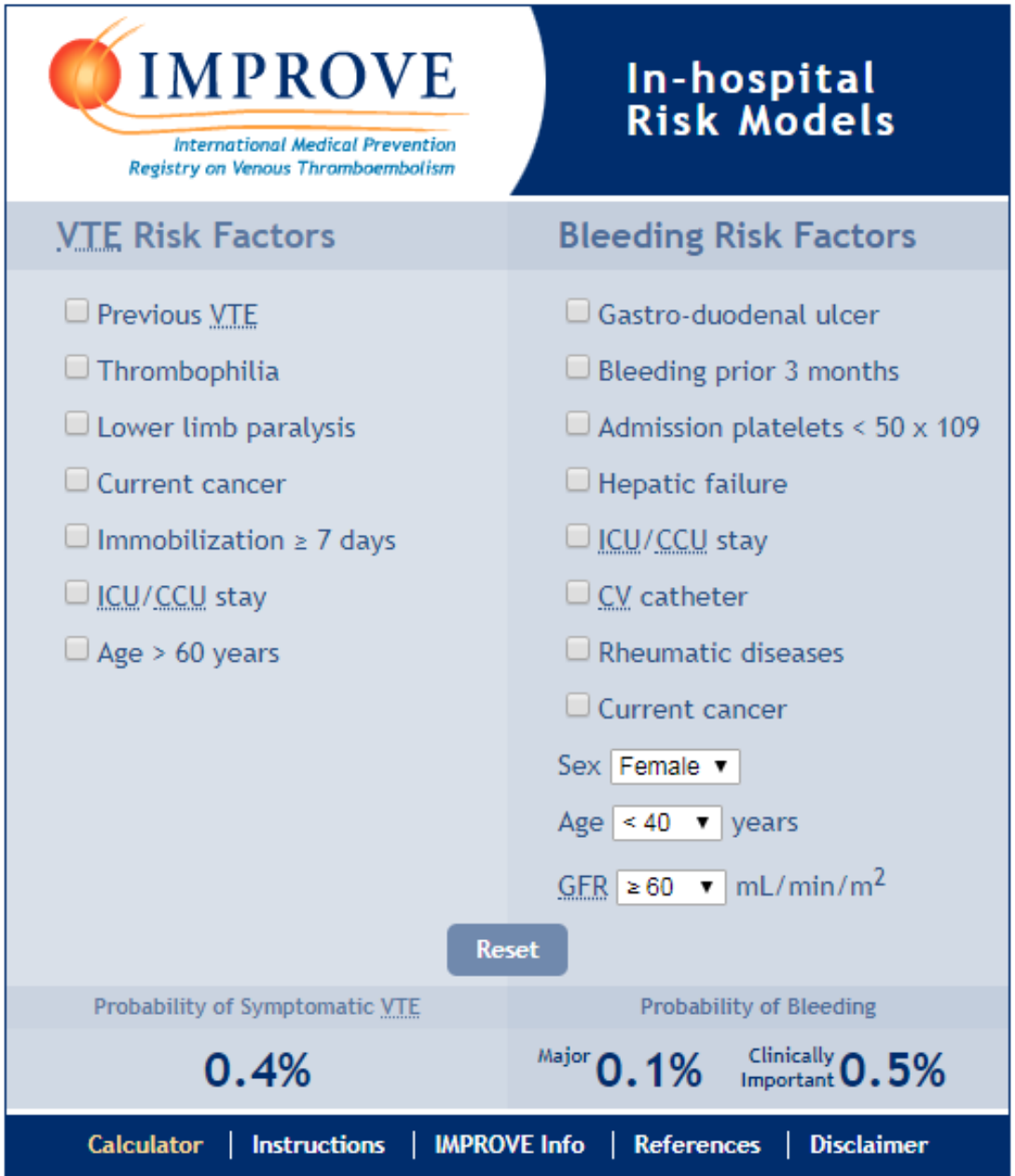
•*Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months. †Bedrest with bathroom privileges (either due to patient's limitations or on physicians order) for at least 3 days. ‡Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

# Padua Prediction score




Barbar et al JTH 2010, 8(11): 2450-2457

# IMPROVE risk assessment tool for medical inpatients




www.outcomes-umassmed.org/IMPROVE/

- World leading national VTE Prevention Programme
- Risk assessment models
  - Validate DoH
  - Which is best RAM? Adults v children
  - Is consistency of RAM important for the national VTE prevention programme?
- How long should we be giving pharmacological prophylaxis to medical and surgical patients?
  - Median LOS medical inpatient 1-2 days
- RCT of aspirin alone in TKR

# Thank you

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