RCT on GCS/LMWH vs LMWH in VTE prophylaxis

GAPS: Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery

A Multi-Centre Randomised Clinical Trial

Joseph Shalhoub, Alun H Davies
on behalf of the GAPS Trial Investigators

Imperial College London

Thrombosis UK
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NHS
National Institute for Health Research

Disclosure

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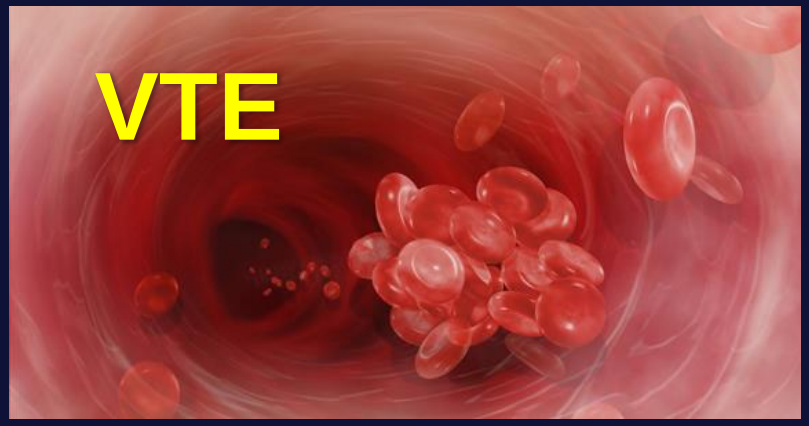
The views and opinions expressed herein do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health

The Clinical Problem



"In the UK pulmonary embolism following DVT in hospitalised patients would cause 25,000 preventable deaths each year if thromboprophylaxis is not given"

Limited evidence for *how* VTE prophylaxis is achieved

- Evidence base supporting UK NICE's recommendations for the use of graduated compression stockings (GCS) for VTE prevention in the UK is rightly challenged as there is a dearth of RCTs to support practice

Whittaker et al. BMJ 2013

- Lack of evidence for the additional benefit of GCS over and above the benefit of low molecular weight heparin (LMWH) alone in this context

Zareba et al. BJS 2014

Systematic Review

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REVIEW ARTICLE

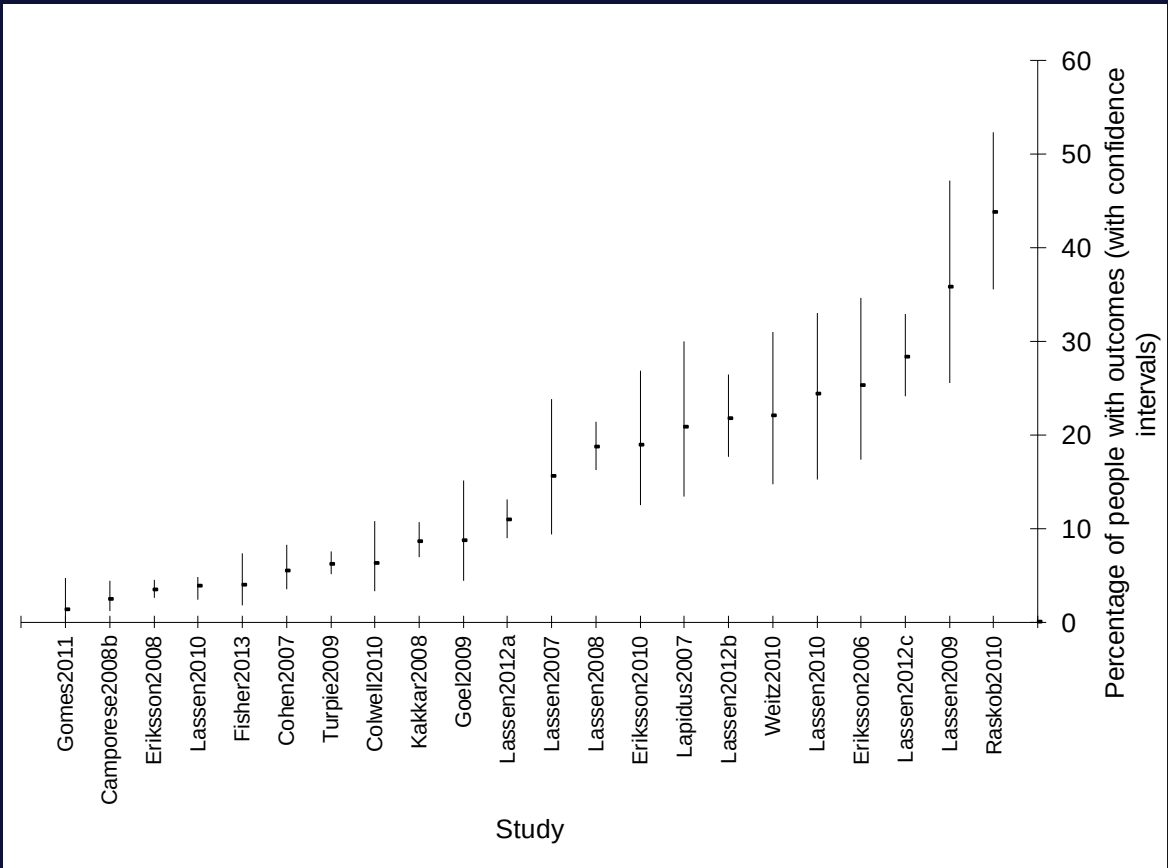
Richard P. Cambria, MD, Section Editor

The additional benefit of graduated compression stockings to pharmacologic thromboprophylaxis in the prevention of venous thromboembolism in surgical inpatients

Rishi Mandavia, BSc, Joseph Shalhoub, PhD, Karen Head, MSc, and Alun H. Davies, DM, *London, United Kingdom*

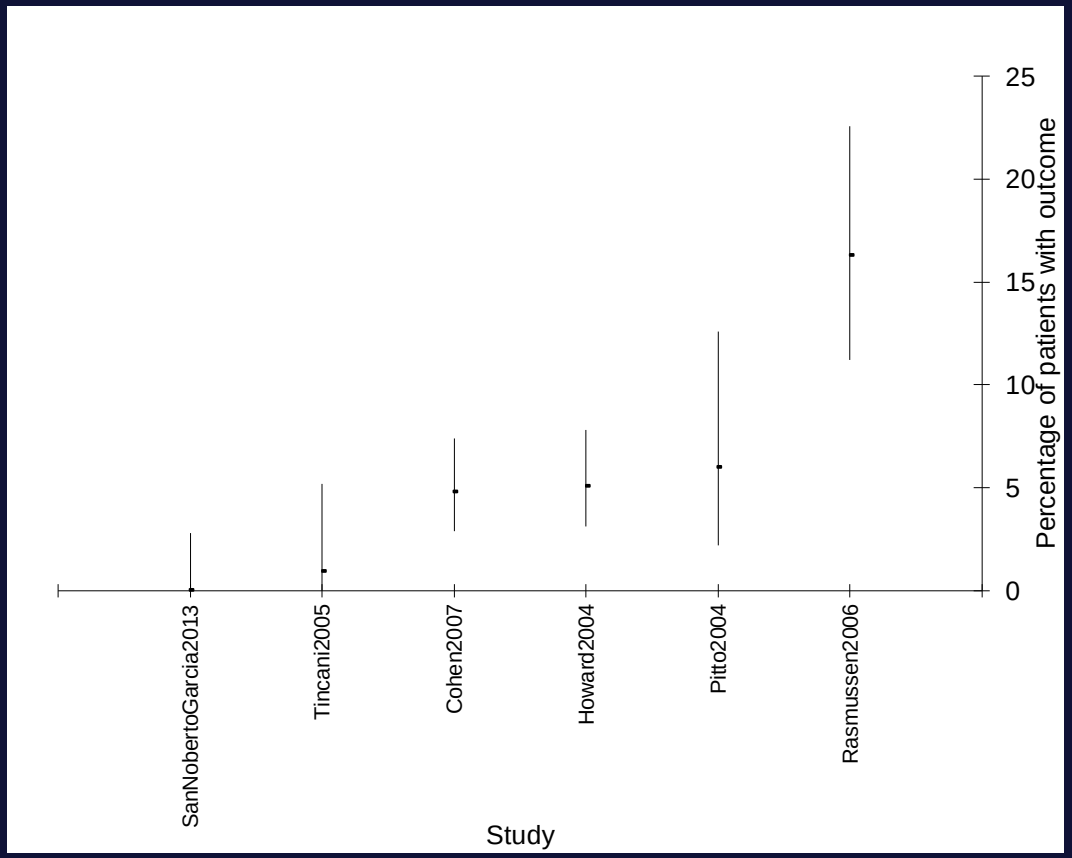
- Single direct comparison between pharmacoprophylaxis and GCS + pharmacoprophylaxis. Hip surgery. No significant difference in VTE
  Cohen et al. *J Bone Joint Surg* 2007;89:887-92
- 22 RCT study **arms**

Pharmacological Thromboprophlyaxis Alone
n=22 study arms



Point estimate of patients with VTE varied from 1.3% to 43.8%

GCS + Pharmacological Thromboprophlyaxis
n=6 study arms



- Point estimate of patients with VTE varied from 0% to 16.3%
- Significant heterogeneity precluded quantitative synthesis

Benefits *vs* Risks

- **If** GCS were to offer a reduction in VTE risk over and above LMWH, these benefits need to be weighed against the risks and disadvantages of GCS

  – Discomfort
  – Ischaemia
  – Blistering
  – Cost
  – Non-compliance
  – Need for staff assistance in wearing

Cost of purchasing and applying GCS to surgical patients in England estimated at £63.1 million per annum

RCT Aim

To determine whether low dose LMWH alone is non-inferior to a combination of GCS and low dose LMWH

for the prevention of VTE

in adult elective surgical patients

identified as being at moderate and high risk for VTE

Study Population

- Elective surgical patients
- Moderate or high risk of VTE according to the UK Department of Health VTE Risk Assessment

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)			

Outcome Measures

Primary Outcome: VTE within 90 days

Duplex ultrasound-proven new lower-limb DVT (symptomatic or asymptomatic)

+

Symptomatic PE (imaging confirmed)

up to 90 days post-randomisation

Secondary Outcomes

- Quality of life – EQ5D
- Compliance with stockings & LMWH
- Overall mortality

Safety Outcomes

- GCS-related complications
- Bleeding complications
- LMWH allergy

Study Design

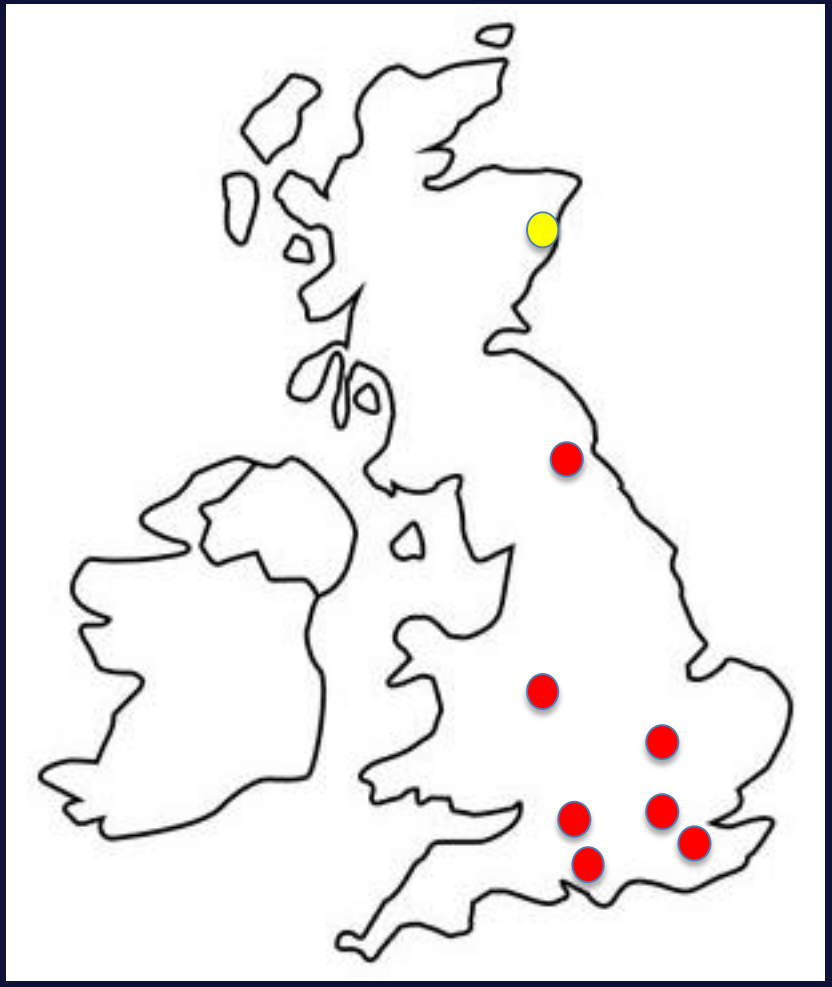
- Seven-centre, UK-wide, open, randomised controlled trial
- Non-inferiority, group sequential trial design

Multi-Centre, Multi-Disciplinary

- Imperial (CI: Prof AH Davies, Co-Is: Dr C Baker, Mr J Shalhoub, Sr K Dhillon)
- Kings (PI: Prof BJ Hunt)
- Cambridge (PI: Mr M Gohel)
- Birmingham (PI: Prof AW Bradbury)
- Newcastle (PI: Prof G Stansby)
- Salisbury (PI: Dr T Everington)
- Southampton (PI: Prof D Warwick)

- CTU: CHaRT, Aberdeen (Co-I: Prof J Norrie)

- Thrombosis UK (Co-I: Ms A Stephens-Boal)



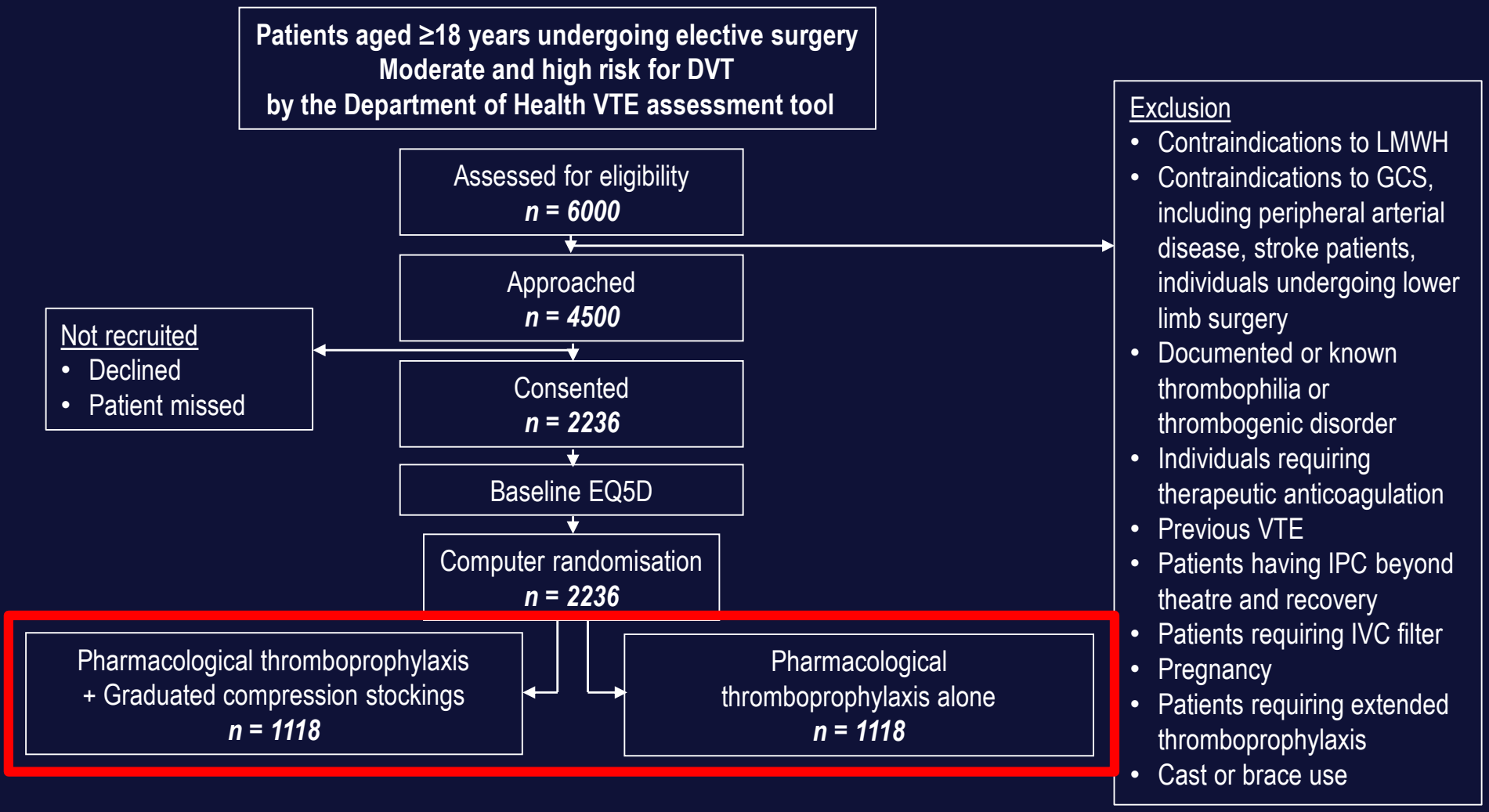
Exclusion Criteria

- Contraindications to LMWH / GCS
- Documented or known thrombophilia / thrombogenic disorder
- Requiring therapeutic anticoagulation
- Previous VTE
- Having intermittent pneumatic compression beyond theatre and recovery
- Pregnancy
- Need extended VTE prophylaxis
- Cast / brace use

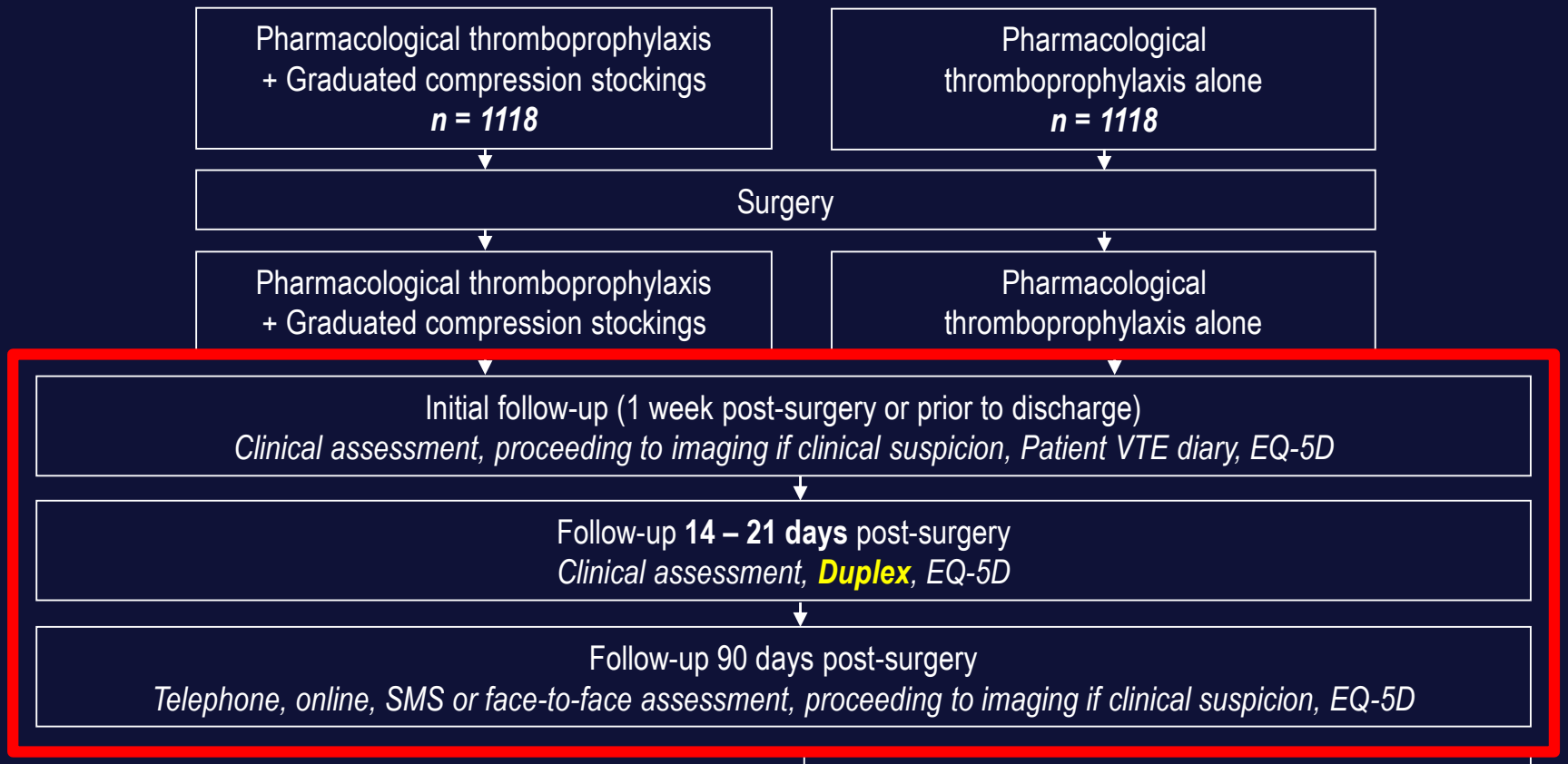
Sample Size

- Assuming an event rate of 6% of VTE at 90 days in the combined group and non-inferiority margin of 3.5%
- Loss to follow up of 10%
- Maximum sample size = 2236

Recruitment



Follow-up



Primary outcome – composite

If clinical VTE confirmed on investigation at any point within 90 days, this will be recorded

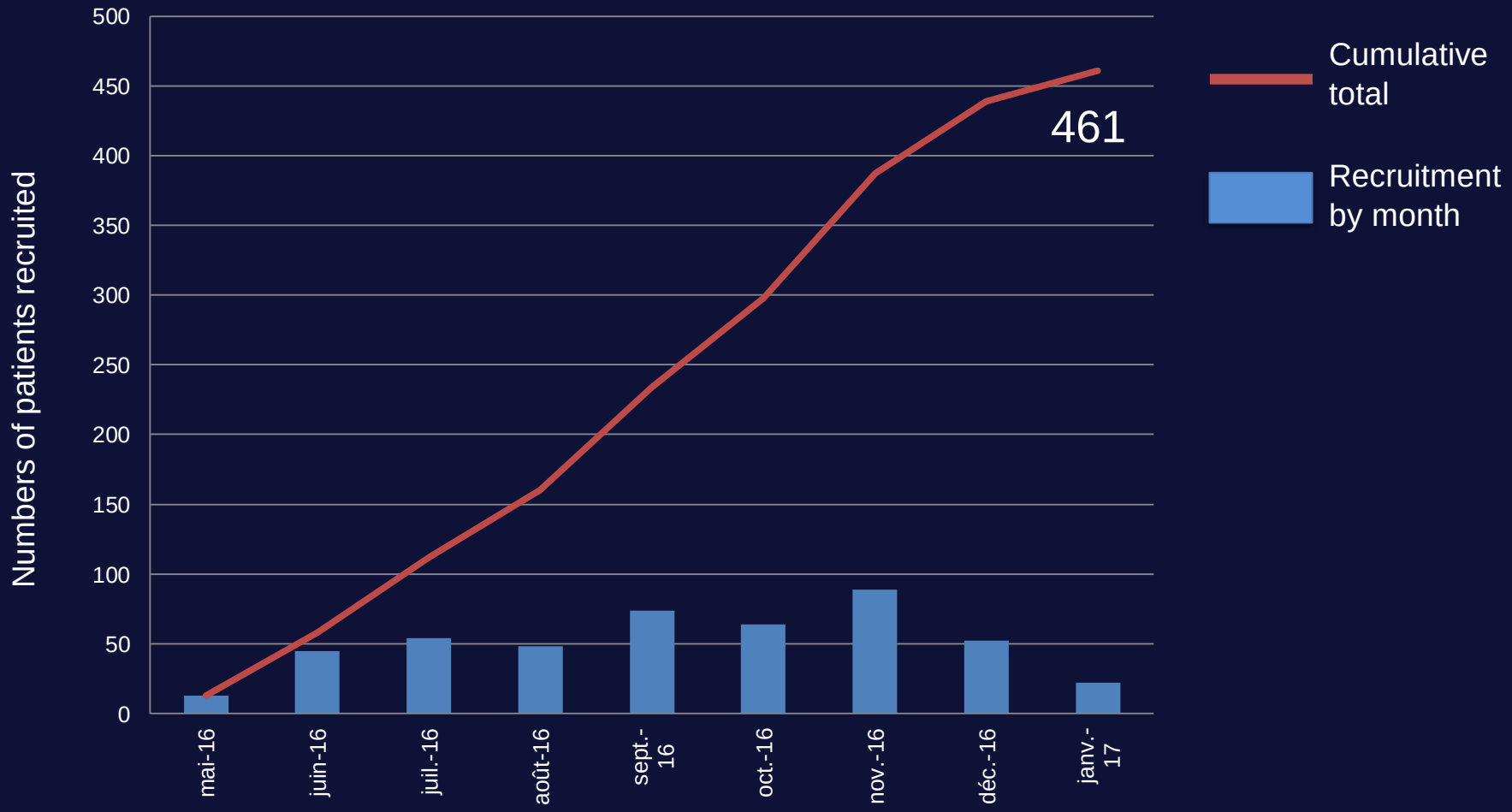
- **Symptomatic DVT**
- **Asymptomatic DVT identified by duplex**
- **Imaging-confirmed symptomatic PE**

Secondary outcome measures

- Quality of life – EQ-5D
- Compliance with stockings
- GEC-related lower limb complications (skin ulceration, ischaemia, …)
- Bleeding complications
- Allergic reactions to LMWH

Trial Progress

- To date 2475 patients screened
- 461 randomised (19% inclusion rate)



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Thank you

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