

Thromboprophylaxis in Lower Limb Immobilisation (TiLLI): a multicentre study comprising two linked open label phase III randomised controlled trials evaluating the effectiveness and cost effectiveness of different methods of pharmacological prophylaxis for patients with temporary lower limb immobilisation.

Submission date 10/05/2024	Recruitment status Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 30/07/2024	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 12/09/2024	Condition category Injury, Occupational Diseases, Poisoning	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

People have an increased risk of blood clots when they have a leg injury treated with a plaster cast or a splint, which happens to over 70,000 people every year in the UK. Blood clots can cause long term problems in the legs and can also move to the lungs, causing serious illness and occasionally death. Medicines are available to reduce the risk of blood clots, but they can also increase the risk of bleeding. In people at high risk of clots, most hospitals use the recommended daily injections which can be uncomfortable and sometimes difficult to give. Tablets are available that reduce the risk of blood clots in other groups, but we don't know if tablets work as well as the injections for people with a leg injury. We also don't know whether people at low risk of blood clots may benefit from any medication.

Our study has two aims - to determine whether giving tablets to people at high risk of clots after a leg injury is as good as injections, and whether giving any medication is better than standard care (advice only) for people at low risk of clots. TiLLI is two linked studies designed to answer these aims.

Who can participate?

Patients aged 16 years or older, placed in temporary lower limb immobilisation (rigid cast or brace) as a result of an injury that occurred within the last 7 days.

What does the study involve?

Participants will be invited who have been placed in a plaster cast or splint after injury and are being assessed for clot risk. People who agree and are at high risk of clots will have either tablets or injections to reduce their risk; those at low risk will receive tablets, injections, or no medication. Patients and doctors will know what medication they are taking. All patients will be provided with written guidance on the signs and symptoms of blood clots and advice on managing their medication.

What are the possible benefits and risks of participating?

Benefits:

Not provided at time of registration

Risks:

TiLLI-Low: the standard of care for participants considered to be low risk for VTE receive no pharmacological prophylaxis. In TiLLI-Low, participants may be randomised to receive routine care (no prophylaxis), Direct Oral AntiCoagulant (DOAC), or Low Molecular Weight Heparin (LMWH). Administration of anticoagulants may induce a propensity for increased bleeding, which may lead to several complications, including: haematuria, melena or haematochezia, pronounced ecchymosis, prolonged episodes of epistaxis, gingival bleeding, haematemesis or haemoptysis, menorrhagia. Major bleeding events and clinically-relevant bleeding events will be monitored throughout the study.

Within the LMWH cohort requiring self-injection, risks such as cutaneous ecchymosis or irritation at the injection site.

TiLLI-high: the standard of care for participants considered to be high risk for VTE is pharmacological prophylaxis in the form of LMWH. In TiLLI-high, participants will be randomised to receive either routine care (LMWH) or DOAC. Use of DOACs are contraindicated in pregnancy and breast feeding, as such we will exclude participants who are pregnant, actively seeking pregnancy, or breast feeding from the study.

Where is the study run from?

Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?

May 2024 to April 2028

Who is funding the study?

National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?

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Contact information

Type(s)

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Additional identifiers**EudraCT/CTIS number**

Nil known

IRAS number

1009305

ClinicalTrials.gov number

NCT06370273

Secondary identifying numbers

V1.0-26/04/24, IRAS 1009305, CPMS 62644

Study information

Scientific Title

Thromboprophylaxis in Lower Limb Immobilisation (TiLLI): a multicentre study comprising two linked open label phase III randomised controlled trials evaluating the effectiveness and cost effectiveness of different methods of pharmacological prophylaxis for patients with temporary lower limb immobilisation.

Acronym

TiLLI

Study objectives

Primary objective:

To estimate and draw inferences on the difference in a composite outcome of net clinical benefit, including symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding) between treatment groups within 90 days of randomisation.

Secondary objectives:

1. To compare all individual components of the primary composite outcome between treatment groups within 42 and 90 days from randomisation
2. To estimate and draw inferences on the difference in complications (including clinically relevant non-major bleeding and surgical site bleeding) between treatment groups within 42 days from randomisation
3. To report adherence to each therapy
4. To estimate and draw inferences on the acceptability of different prophylactic anticoagulants using the Anti Clot Treatment Scale (ACTS)
5. To estimate and draw inferences on differences in quality-of-life measures, including quality of life-adjusted survival, between treatment groups, up to 90 days post randomisation
6. To estimate and draw inferences on the difference in hospital readmission/reattendance and medication use (specific to VTE and bleeding) between treatment groups within the first 90 days
7. To estimate the health and social care resource use and costs and the relative cost effectiveness between arms
8. To estimate longer term outcomes, such as post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and bleeding complications and draw inferences on cost effectiveness, by using a previously developed decision analytic model, informed by directly measured events up to 90 days

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 22/07/2024, North West – Liverpool Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8340; liverpoolcentral.rec@hra.nhs.uk), ref: 24/NW/0166

Study design

Interventional randomized parallel-group controlled trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Safety, Efficacy

Participant information sheet**Health condition(s) or problem(s) studied**

Venous thromboembolism (VTE) in population with temporary lower limb immobilisation following injury

Interventions

TiLLI study consists of 2 linked randomised controlled trials: TiLLI-High and TiLLI-Low. Participants suitability for TiLLI-High and TiLLI-Low will be established during screening, participants will be randomised using Sealed Envelope. Participants in TiLLI-High will be allocated to either parenteral drug treatment (a) or oral drug treatment (b). Participants in TiLLI-Low will be allocated to treatment (a) or (b), or no drug prophylaxis (c). Site teams are permitted to choose which IMP within the treatment group to use. Drug treatments will be provided for the duration of immobilisation or up to 42 days (whichever is earlier).

a) Parenteral drug treatment

- Enoxaparin 40mg once daily via subcutaneous injection
- Tinzaparin 4500 IU once daily via subcutaneous injection
- Dalteparin 5000 IU once daily via subcutaneous injection
- Fondaparinux 2.5mg once daily via subcutaneous injection

b) Oral drug treatment

- Rivaroxaban 10mg OD via oral ingestion
- Apixaban 2.5mg BD via oral ingestion

c) No drug prophylaxis (TiLLI-Low only)**Intervention Type**

Drug

Pharmaceutical study type(s)

Pharmacoeconomic, Prophylaxis, Therapy

Phase

Phase III

Drug/device/biological/vaccine name(s)

Rivaroxaban, apixaban, enoxaparin sodium, tinzaparin sodium, dalteparin sodium, fondaparinux sodium

Primary outcome measure

A composite primary outcome of net clinical benefit, comprising symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death

from either pulmonary embolus or major bleeding) within 90 days used as a binary variable ('1' if any event occurred, '0' if none of the events occurred).

Secondary outcome measures

1. All individual components of the composite outcome as binary variables ('1' if any event occurred, '0' if no event occurred) of an event happening within 42 days of randomisation for a) major bleeding events and within 90 days for b) symptomatic pulmonary embolism or symptomatic deep vein thrombosis and c) cause-specific mortality
2. Patient satisfaction regarding the burdens and benefits of anticoagulation, using the validated Anti-Clot Treatment Scale (ACTS) for patients allocated to drug treatments, measured 42 days after randomisation
3. Health utility (EQ-5D-5L): differences in EQ-5D-5L QoL utility at 7 days, 42 days and 90 days after randomisation compared to a retrospective baseline and QALYs within 90 days of randomisation
4. Medication adherence: monitor participant adherence to allocated anti-coagulant verified through a digital response system, measured at 7 days, 14 days, 21 days, 28 days, 35 days, and 42 days after randomisation
5. Complications including clinically relevant non-major bleeding and surgical site bleeding, objectively defined by ISTH criteria, reported throughout up until 42 days after randomisation
6. Hospital readmission/reattendance using bespoke Case report forms and review of EHR, research staff to collect information on resources required to deliver subsequent care reviews (including scheduled clinic and unscheduled hospital attendance), and investigations within the first 90 days after randomisation
7. Health and social care resource use, using bespoke Case Report Forms and review of EHR, research staff to collect information on health and social care resource use within the first 90 days after randomisation
8. Patient longer-term outcome VTE and bleeding data, using an existing VTE model with risk-adjusted, population-specific effect estimates from this study, informed by directly measured events up to 90 days after randomisation

Overall study start date

08/05/2024

Completion date

30/04/2028

Eligibility

Key inclusion criteria

1. Age ≥ 16 years
2. Placed in temporary lower limb immobilisation (rigid cast or brace) as a result of an injury that occurred within the last 7 calendar days

Participant type(s)

Patient

Age group

Adult

Lower age limit

16 Years

Sex

Both

Target number of participants

10,044

Key exclusion criteria

1. Hospital admission is required direct from the emergency department, minor injuries unit, or fracture clinic setting with an expected length of stay >2 calendar days.
2. Absolute contraindication or known hypersensitivity to anticoagulants, including history of end stage renal failure (eGFR <20ml/min/1.73m²), hepatic failure or use of concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g. ritonavir) or active substances strongly inhibiting elimination pathways such as CYP3A4 or P-gp (such as clarithromycin, erythromycin or dronaderone) or a history of heparin induced thrombocytopenia.
3. Pregnancy, actively seeking conception, or active breastfeeding.
4. Preceding use of anticoagulant treatment for >3 calendar days at prophylactic or therapeutic dose
5. Previous enrolment in the TiLLI study.
6. Non-rigid immobilisation (crepe bandage, tubigrip support, strapping).
7. Time since prescription of rigid immobilisation >3 calendar days.
8. Co-enrolment onto a CTIMP where an anticoagulant is administered.
9. People lacking the capacity to consent.
10. Inability or refusal to use acceptable contraception up until after the last administration of IMP. Only applicable for women of childbearing potential who have been randomised to receive apixaban or rivaroxaban

Date of first enrolment

01/10/2024

Date of final enrolment

31/01/2028

Locations**Countries of recruitment**

England

Scotland

United Kingdom

Wales

Study participating centre

The Royal London Hospital

The Royal London Hospital

Alexandra House

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Study participating centre
Newham University Hospital NHS Trust
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Study participating centre
Wythenshawe Hospital
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Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities
No participant identifiable data will be included in publications. All study data will be linked to study ID alone.

Intention to publish date

30/04/2029

Individual participant data (IPD) sharing plan

Data will be collected in the OpenClinica4 study database and extracted to the BCC Data Safe Haven (DSH). The BCC DSH is accessible upon request to individuals with a proven and approved requirement for access (i.e., study statistician, study health economist). Raw data will not be made publicly accessible. Study data will be pseudo-anonymised using unique participant ID's, it is prohibited to attempt to identify participants from the participant ID. Participant consent will be in place for collecting study data.

IPD sharing plan summary

Not expected to be made available