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Rivaroxaban for stroke patients with antiphospholipid syndrome

Submission date
26/03/2019

Recruitment status
No longer recruiting

Registration date
25/04/2019

Overall study status
Completed

Last Edited
03/03/2025

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The RISAPS trial follows on from the RAPS (Rivaroxaban in Antiphospholipid Syndrome) study that showed that rivaroxaban could offer a potentially effective alternative to warfarin for patients with antiphospholipid syndrome (APS) who have thrombosis (blood clots) in their veins, rather than in their arteries and require standard intensity anticoagulation (blood thinning). Currently, APS patients who have had an ischaemic stroke (which occurs when blood flow to an area of brain is cut off) are treated with warfarin to reduce the risk of a recurrence. Warfarin tends to have a variable ‘blood thinning’ effect in patients with APS, necessitating frequent (usually weekly) INR blood tests to monitor the effect of the warfarin, which is inconvenient for patients.
The RISAPS trial will compare high intensity (high dose) rivaroxaban versus high intensity warfarin (current standard of care treatment) for 24 months, in APS patients, with or without lupus (systemic lupus erythematosus; SLE), requiring anticoagulation after experiencing a stroke, a 'mini stroke' (also known as a transient ischaemic attack) or other ischaemic brain damage (caused by blood clots in the brain arteries or smaller blood vessels).
Rivaroxaban, unlike warfarin, does not require regular blood tests, because it has a more predictable blood thinning effect. Furthermore, rivaroxaban does not interact with food or alcohol and has fewer interactions than warfarin with other drugs. If rivaroxaban is no worse than warfarin for anticoagulation of APS patients with stroke or other ischaemic brain manifestations, it could become the standard of care for the treatment of APS patients, with or without lupus, who have experienced stroke or other ischaemic brain manifestations, and improve patients' quality of life.
The European Medicines Agency recommended, in 2019, against the use of DOACs, which include rivaroxaban, in individuals with a history of thrombosis (blood clots) who have APS, especially in patients with triple positive antiphospholipid antibodies. This recommendation, which has been adopted by other regulatory authorities, refers to the current (standard intensity) doses of DOACs prescribed for long term use. Importantly, the RISAPS trial is using high intensity rivaroxaban to ‘match’ high intensity warfarin (standard of care treatment). The trial will not include individuals who have triple positive antiphospholipid antibodies (i.e., lupus anticoagulant, anticardiolipin and anti-beta 2 glycoprotein I antibodies) – such individuals may be allowed in the study, in due course, only if the Independent Data Monitoring Committee confirms that it is safe for them to take part in RISAPS and receive a high dose of rivaroxaban.

Who can participate?
Stroke patients with antiphospholipid syndrome

What does the study involve?
Participants are randomly allocated to take either rivaroxaban or warfarin for 24 months. All participants undergo a series of assessments, including an MRI brain scan, at the start and the end of the study (i.e. after 24 months) and the research teams also record all safety related events, including any thrombosis or bleeding, that occur during the trial period.

What are the possible benefits and risks of participating?
Taking part in this trial may or may not benefit participants directly. Participants may be helping to improve treatment for all APS patients in the future. After the trial results are available, we should know if rivaroxaban is as effective as warfarin for stroke patients with APS, with or without lupus.

Where is the study run from?
University College London Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
March 2019 to February 2025

Who is funding the study?
Versus Arthritis (formerly known as Arthritis Research UK)

Who is the main contact?
RISAPS@ucl.ac.uk

Study website
https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/

Contact information

Type(s)
Public

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Type(s)
Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2018-001735-49

IRAS number
248593

ClinicalTrials.gov number
NCT03684564

Secondary identifying numbers
CTU/2015/1974, IRAS 248593

Study information

Scientific Title
Rivaroxaban versus warfarin for stroke patients with antiphospholipid syndrome, with or without SLE (RISAPS): a randomised, controlled, open-label, phase IIb, non-inferiority proof of principle trial

Acronym
RISAPS

Study objectives
Current hypothesis as of 19/07/2021:

We hypothesise high-intensity oral rivaroxaban (15mg twice daily) is non-inferior to high intensity warfarin (target international ratio [INR] 3.5 (range 3.0-4.0]) for the secondary prevention of stroke, transient ischaemic attack (TIA) or other ischaemic brain manifestations in patients with antiphospholipid syndrome (APS). These are currently unlicensed indications for rivaroxaban and other direct oral anticoagulants (DOACs).

We therefore propose to establish a) non-inferiority in the efficacy of rivaroxaban compared with that of warfarin; and b) absence of safety signals. We believe that this would provide sufficient supporting data to change practice for our patients, i.e., to make rivaroxaban the

standard of care for the treatment of APS patients, with or without SLE, who have stroke or other ischaemic brain manifestations.

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Previous hypothesis:

It is hypothesised that rivaroxaban is non-inferior to warfarin for the secondary prevention of ischaemic stroke or other ischaemic brain manifestations in patients with antiphospholipid syndrome (APS). These are currently unlicensed indications for rivaroxaban and other direct oral anticoagulant (DOACs).

Clinically, the hypothesis is that in patients with thrombotic APS with ischaemic stroke, TIA or other ischaemic brain manifestations, the efficacy of high intensity rivaroxaban would be no worse than that of high intensity warfarin.

The researchers therefore propose to establish a) non-inferiority in the efficacy of rivaroxaban compared with that of warfarin; and b) absence of safety signals. They believe that this would provide sufficient supporting data to change practice for patients, i.e. to make rivaroxaban the standard of care for the treatment of APS patients, with or without systemic lupus erythematosus (SLE), who have stroke or other ischaemic brain manifestations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/06/2019, London Dulwich Ethics Committee (Ground Floor, Skipton House, 80 London Road, London, SE1 6LH, UK; +44(0)20 797 22567; dulwich.rec@hra.nhs.uk), ref: 19/LO /0201

Study design
Randomized controlled open-label non-inferiority Phase IIb proof of principle clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a copy of the participant information sheet.

Health condition(s) or problem(s) studied
Stroke patients with antiphospholipid syndrome with or without systemic lupus erythematosus

Interventions
Current interventions as of 05/02/2025:

Phase IIb Trial, 40 patients will be randomised with a ratio of 1:1 to receive either:
• Rivaroxaban 15mg twice daily orally for 24 months or
• Warfarin (standard of care in the RISAPS trial) to maintain a target INR of 3.5 (range 3.0-4.0) for 24 months.

Previous interventions as of 19/07/2021:

140 patients will be randomised with a ratio of 1:1 to receive either:
• Rivaroxaban 15mg twice daily orally for 24 months or
• Warfarin (standard of care in the RISAPS trial) to maintain a target INR of 3.5 (range 3.0-4.0) for 24 months.

Previous interventions:

Patients will be randomised to receive either:
1. Rivaroxaban 15 mg twice daily for 24 months
2. Warfarin (as per standard care for the trial sites) to maintain a target INR of 3.5 (range 3.0-4.0) for 24 months
Patients will be randomised with a ratio of 1:1

WMH will be used as a surrogate marker of ischaemic damage (stroke), as there are relatively few APS stroke patients, possibly due to underdiagnosis, and recurrent stroke and other clinical cerebral events in APS patients are rare in clinical practice because of effective anticoagulation. Measurements of WMH volume have successfully been used in longitudinal studies of cerebral SVD and SLE.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Warfarin, rivaroxaban

Primary outcome measure
Current primary outcome measure as of 19/07/2021:

To compare the efficacy of high-intensity oral rivaroxaban (15mg twice daily) vs high-intensity warfarin, target INR 3.5 (range 3.0-4.0), in patients with APS with or without SLE who have had a stroke or other ischaemic brain manifestations.
The comparison of efficacy will be based on the rate of change in brain white matter hyperintensity (WMH) volume on MRI, a surrogate marker of ischaemic damage, between baseline and 24 months follow up.

Previous primary outcome measure:

Efficacy based on the rate of change in brain white matter hyperintensity (WMH) volume on MRI, a surrogate marker of ischaemic damage, between baseline and 24 months follow-up.

Secondary outcome measures

1. Efficacy
1.1. Neuroradiological markers
1.1.1. Mean diffusivity and fractional anisotropy as a measure of microstructural white matter damage derived from diffusion tensor imaging (DTI)
1.1.2 Changes in total brain volume, white matter volume and grey matter volume on T1 weighted volumetric images
1.1.3. Brain infarcts
1.2. Cortical or subcortical
1.3. Assessment of volume
1.4. Cerebral venous occlusions
All neurological secondary outcomes will be assessed using data from the MRI scans and additional information from the cognitive function assessment using the MoCA and the Queens Square assessment tool kit. MRIs will carried out at baseline and 24 months. Assessment tools will be administered at baseline, day 42, 6, 12, 18 & 24 month clinic visits.

2. Clinical
2.1. Vascular events
2.1.1. Ischaemic stroke or transient ischaemic attack (TIA)
2.1.2. Occlusive arterial events in other sites including systemic embolism
2.1.3. Cerebral venous thrombosis
2.1.4. Venous thromboembolism in other sites
2.1.5. Microvascular thrombosis
2.1.6. Superficial venous thrombosis
2.2. Death
2.3. Composite clinical outcomes
2.3.1. A composite of all thrombotic events: arterial, venous, microvascular, and death
2.3.2. Major adverse cardiac and cerebrovascular events (MACCE)
2.4. The rate of change in cognitive function assessed using the Montreal Cognitive Assessment (MoCA) (added 19/07/2021) in conjunction with the Queen Square Cognitive Assessment score.

3. Safety
3.1. Bleeding: all bleeding events: major, clinically relevant non-major or minor
3.2. Serious adverse events other than major bleeding
3.3. Cerebral microbleeds (CMB) assessed with susceptibility-weighted imaging (SWI) as a surrogate marker of bleeding risk

For clinical and safety outcomes, this data will be collected on case report forms at clinical visits, and on a participant diary card only for recording minor events, such as a minor bleed. Any major of clinically significant events will be reported as per standard UK safety reporting timelines for Serious Adverse Events. So when 24 hours of the site becoming aware. Adverse events will also be recorded at study visits or when reported to the site by the participant. These type of events

will be recorded on specific reporting forms. A summary of the number of type of these events will be done monthly by the team and reported to our independent data monitoring committee every 6 months or before if an event is deemed serious enough.

4. Health economics - resource use collected from the participant self-report and medical records at baseline and then at 6, 12, 18 & 24 month follow-up visits
4.1. Quality of life (QoL) assessed using EQ-5D-5L self-completed by participants
4.2. Health and social care resource use assessed using trial follow-up visit case report forms (CRFs)
4.3. Mean incremental cost per quality-adjusted life year (QALY)

5. Anticoagulation intensity
5.1. Rivaroxaban
5.1.1. Rivaroxaban anti-Xa levels
5.2. Warfarin
5.2.1. Time in target therapeutic range (TTR)
5.2.2. Amidolytic factor X as a lupus anticoagulant independent assessment of warfarin anticoagulant effect

6. Exploratory outcomes
6.1. Rivaroxaban pharmacokinetic (PK) modelling
6.2. Cerebral blood flow (CBF) derived from MR perfusion imaging using an arterial spin labelling (ASL) technique
Exploratory outcomes use data from blood samples collected at each follow-up visit and from the MRI images

Overall study start date
01/03/2019

Completion date
03/02/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 28/11/2022:

1. Patients must be confirmed as having persistent antiphospholipid antibodies (aPL), defined as: positivity of one or more aPL, i.e. lupus anticoagulant, IgG and/or IgM anticardiolipin and/or anti beta 2 glycoprotein I antibodies at >40 GPL or MPL units or > the 99th centile of normal, on two or more occasions, at least 12 weeks apart.
2. One or more of: a) Ischaemic stroke; b) transient ischaemic attack (TIA) with evidence of either acute or chronic ischaemic injury on brain magnetic resonance imaging (MRI) (including diffusion-weighted magnetic resonance imaging (DWI) lesion(s), previous cortical or subcortical infarction (s), or white matter hyperintensities) and diagnosed by a clinician with expertise in stroke; c) brain infarcts (territorial or subcortical) or white matter hyperintensities (WMH) of presumed vascular origin on brain MRI, with or without cognitive impairment; and an expert clinical opinion that anticoagulation is a reasonable treatment option (with the aim of preventing ischaemic brain injury).

3. Patients must weigh ≥ 50kg and ≤ 135kg
4. Women must be on adequate contraception, barrier or hormonal, unless postmenopausal or sterilised

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Previous inclusion criteria as of 19/07/2021:

1. Patients must be confirmed as having persistent antiphospholipid antibodies (aPL), defined as: positivity of one or more aPL, i.e. lupus anticoagulant, IgG and/or IgM anticardiolipin and/or antibeta 2 glycoprotein I antibodies at > 40 GPL or MPL units or > the 99th centile of normal, on two or more occasions at least 12 weeks apart.
2. One or more of: a) Ischaemic stroke; b) transient ischaemic attack (TIA) with evidence of either acute or chronic ischaemic injury on brain MRI (including diffusion-weighted magnetic resonance imaging (DWI) lesion(s), previous cortical or subcortical infarction(s), or white matter hyperintensities) and diagnosed by a clinician with expertise in stroke; c) brain infarcts (territorial or subcortical) or white matter hyperintensities (WMH) of presumed vascular origin on brain MRI, with or without cognitive impairment; and an expert clinical opinion that anticoagulation is a reasonable treatment option (with the aim of preventing ischaemic brain injury).
3. Women must be on adequate contraception, barrier or hormonal, unless postmenopausal or sterilised.

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1. Patients must be confirmed as having persistent antiphospholipid antibodies (aPL), defined as: positivity of one or more aPL, i.e. lupus anticoagulant, IgG and/or IgM anticardiolipin and/or anti beta 2 glycoprotein I antibodies at >40 GPL or MPL units or > the 99th centile of normal, on at least two consecutive occasions at least 12 weeks apart. Criteria for the laboratory diagnosis of aPL are detailed in Appendix 3 of the Protocol.
2. One or more of: a) ischaemic stroke; b) transient ischaemic attack (TIA) with evidence of either acute or chronic ischaemic injury on brain MRI (including DWI lesion(s), previous cortical or subcortical infarction(s), or white matter hyperintensities (WMH)) and diagnosed by a clinician with expertise in stroke; c) brain infarcts (territorial or subcortical) or WMH of presumed vascular origin on brain MRI, with or without cognitive impairment; and an expert clinical opinion that anticoagulation is a reasonable treatment option (with the aim of preventing ischaemic brain injury).
3. Women must be on adequate contraception, barrier or hormonal, unless postmenopausal or sterilised.
NB: patients weighing <50 kg or >120 kg may be included in RISAPS on a case by case basis, following assessment by the Investigator and discussion with the CI/delegate before enrolment.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
40

Total final enrolment
43

Key exclusion criteria
Current exclusion criteria as of 28/11/2022:
1. Patients who are triple positive for antiphospholipid antibodies (presence of lupus anticoagulant, IgG and/or IgM anticardiolipin and anti beta 2 glycoprotein I antibodies at >40 GPL or MPL units or > the 99th centile of normal*. (*patients who have previously been triple aPL-positive and have single or double aPL positivity on at least 2 occasions over at least 6 months, including once within 1 month prior to randomisation, can be recruited to the trial)
2. Pregnant or lactating women
3. Severe renal impairment with creatinine clearance < 30 mL/min (i.e. 29 mL/min or less)
4. Liver function tests ALT > 3 x ULN
5. Cirrhotic patients with Child Pugh B or C
6. Thrombocytopenia (platelets < 75 x 109/L)
7. Non-adherence on warfarin (based on clinical assessment)
8. Patients taking strong inhibitors of both CYP3A4 and P-gp pathways such as
8.1. Systemic azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole)
8.2. Patients on human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir)
9. Patients on strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
10. Patients on dronedarone
11. Patients on levetiracetam, sodium valproate/valproic acid, oxcarbazepine or topiramate
12. Patients less than 18 years of age
13. Refusal to consent to the site informing General Practitioner (GP) and Healthcare Professional responsible for anticoagulation care of the participant.
14. Contraindications to MRI (e.g. cardiac pacemaker, severe claustrophobia, inability to lie flat: patients who do not meet local safety rules for MRI).
15. Patients at high risk of bleeding and not suitable for anticoagulation therapy.
16. Previous known allergy or intolerance to warfarin or rivaroxaban.
17. Women planning to become pregnant within the 2-year follow-up period.
18. Patients with known galactose intolerance, total lactase deficiency or galactose malabsorption.
19. Patients who have had active cancer (excluding non-melanoma skin cancers) within the last 2 years
20. Any other reason that the PI or delegate considers would make the patient unsuitable to enter RISAPS

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Previous exclusion criteria as of 19/07/2021:
1. Pregnant or lactating women
2. Severe renal impairment with creatinine clearance <30 mL/min (i.e. 29 mL/min or less)
3. Liver function tests ALT >3 x ULN
4. Cirrhotic patients with Child Pugh B or C
5. Thrombocytopenia (platelets <75 x 10^9/L)
6. Non-adherence on warfarin (based on clinical assessment)
7. Patients taking strong inhibitors of both CYP3A4 and P-gp pathways such as
a. Systemic azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole)

b. Patients on human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir)
8. Patients on strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
9. Patients on dronedarone
10. Patients less than 18 years of age
11. Refusal to consent to the site informing General Practitioner and Healthcare Professional responsible for anticoagulation care of the participant
12. Contraindications to MRI (e.g. cardiac pacemaker, severe claustrophobia, inability to lie flat: patients who do not meet local safety rules for MRI).
13. Patients at high risk of bleeding and not suitable for anticoagulation therapy.
14. Previous known allergy or intolerance to warfarin or rivaroxaban.
15. Women planning to become pregnant within the 2-year follow-up period.
16. Patients with known galactose intolerance, total lactase deficiency or galactose malabsorption.
17. Any other reason that the PI considers would make the patient unsuitable to enter RISAPS.

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Previous exclusion criteria:
1. Pregnant or lactating women
2. Severe renal impairment with creatinine clearance (Cockcroft & Gault) <30 mL/min (i.e. 29 mL /min or less)
3. Liver function tests ALT > 3 x ULN
4. Cirrhotic patients with Child Pugh B or C
5. Thrombocytopenia (platelets < 75 x 109/L)
6. Non-adherence on warfarin (based on clinical assessment)
7. Patients taking strong inhibitors of both CYP3A4 and P-gp pathways such as:
7.1. Systemic azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole)
7.2. Patients on HIV protease inhibitors (e.g. ritonavir)
8. Patients on strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
9. Patients on dronedarone
10. Patients less than 18 years of age
11. Refusal to consent to the site informing GP and healthcare professional responsible for anticoagulation care of participation
12. Contraindications to MRI (e.g. cardiac pacemaker, severe claustrophobia, inability to lie flat: patients who do not meet local safety rules for MRI)
13. Patients at high risk of bleeding and not suitable for anticoagulation therapy.
14. Previous known allergy or intolerance to warfarin or rivaroxaban
15. Patients with known galactose intolerance, total lactase deficiency or galactose malabsorption

Date of first enrolment
09/07/2021

Date of final enrolment
14/11/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
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NW1 2PG

Study participating centre
Imperial College Health Care NHS Trust
Hammersmith Hospital
150 Du Cane Rd
White City
London
United Kingdom
W12 0HS

Study participating centre
Barts Health NHS Trust
Haematology Non-Malignant Clinical Research
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E1 2ES

Study participating centre
Kings College Hospital Foundation Trust
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre
Barking, Havering and Redbridge University Hospitals NHS Trust
Queens Hospital

Rom Valley Way
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United Kingdom
RM7 0AG

Study participating centre
Epsom and St Helier University Hospitals NHS Trust
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Sponsor type
University/education

Website
https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Versus Arthritis

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trial protocol will be made available for public access throughout the trial period. The results of the trial will be disseminated regardless of the direction of effect. The publication of results will comply with the UCL and UCL CCTU Publication Policies and will include submission to open access journals.

Intention to publish date
01/08/2025

Individual participant data (IPD) sharing plan
Participant level data will be stored securely on UCL CCTU servers. This dataset will not be made public in its raw form to protect the participant's identities and to comply with data protection. A fully anonymised dataset will be made available to researchers on submission and review of a formal request, sent in writing to UCL CCTU and the RISAPS Trial Chief Investigator.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No