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Targeted use of low-dose colchicine in patients with coronary artery disease and high clinical risk

Submission date	**Recruitment status**	[X] Prospectively registered
21/03/2024	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/05/2024	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
17/06/2024	Circulatory System	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Despite recent advances, coronary artery disease (CAD) remains the main cause of death worldwide. CAD occurs when the arteries bringing blood to your heart become narrowed by a build-up of fatty material within their walls. If this occurs gradually, it can cause chest discomfort i.e., angina. In a heart attack, the artery wall becomes inflamed and splits causing blood clot formation and an abrupt blockage of flow, resulting in severe pain and damaged heart muscle. Current treatments focus on reducing cholesterol, slowing the build-up of fatty material, and rapidly restoring blood flow during a heart attack. Chronic inflammation, acting in tandem with other risk factors, has been identified as playing a central role in CAD progression and its acute manifestations. Colchicine is a safe, well-tolerated, anti-inflammatory therapy used in the treatment of gout and other inflammatory conditions. Daily treatment with low-dose colchicine has proven effective in reducing rates of heart attack and death in large clinical trials, but use in routine practice remains low. A contributing factor to this reticence is uncertainty regarding the mechanism through which colchicine provides benefit. This study is designed to address this knowledge gap.

Who can participate?

Patients aged 18 to 90 years old with coronary artery disease and high clinical risk

What does the study involve?

Using traditional markers of clinical risk and state-of-the-art imaging from inside the coronary artery, the researchers will identify patients with CAD and the greatest clinical risk. Eligible patients, already established on statin therapy will be allocated to a six-month course of low-dose colchicine plus usual care, or usual care only. Researchers, participants, and usual clinicians will be aware of the allocation during the study.

After 6 months, the researchers will assess the impact of colchicine on the appearance of individual coronary artery lesions, blood flow in the large and small blood vessels of the heart and markers of immune cell function. This study will provide a detailed assessment of colchicine and its mechanism of action in CAD.

What are the possible benefits and risks of participating?
All patients recruited to the study will undergo an additional invasive cardiac catheterisation procedure, with an assessment with multimodality intracoronary imaging. There are known risks associated with this procedure including vascular and bleeding complications. In a recent study with a similar trial design (PACMAN-AMI), about 1% of patients experienced a complication associated with the invasive procedure (i.e., two cases of cardiac arrhythmia, two cases of coronary artery spasm and two cases of air emboli), none of which resulted in significant morbidity. Patients will be actively monitored for these complications and treated as needed. The invasive cardiac catheterisation procedure will involve an additional radiation dose to ensure adequate visualisation of the coronary arteries and safe placement of equipment.
Blood samples (50 ml) will be taken at baseline and at a 6-month follow-up for the planned leukocyte function sub-study. The baseline blood test (20 ml or 4 teaspoons) is carried out as part of routine care - a further 30 ml or 6 teaspoons of blood will be sampled for the additional research blood tests. Blood will be drawn (20 ml or 4 teaspoons) at 90 days to monitor blood cell counts, kidney function and liver function - this will be additional to standard of care. At 6 months, prior to the repeat angiogram, 50 ml of blood (or 10 teaspoons) will be drawn in order to assess blood counts, kidney function, liver function and immune cell function. This will be additional to usual standard care. Theoretically, this carries a potential risk for bleeding, infection and thrombophlebitis but these events are rare.
For participants in the intervention arm, there is a small potential harm associated with chronic colchicine use, namely gastrointestinal upset (1-10:100), increased risk of infection (<1:1000) and blood dyscrasia (<1:1000). Contemporary data from two large clinical trials (COLCOT, LoDoCo2) confirm that complications related to low-dose Colchicine (i.e., 0.5 mg once daily) in patients with chronic coronary syndromes are rare. Participants will be monitored for adverse effects and will have clear guidance on how to contact the research team should concerns arise.

Where is the study run from?
King's College Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
March 2024 to October 2025

Who is funding the study?
King's College Hospital NHS Foundation Trust - Cardiac Research Charity (UK)

Who is the main contact?
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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007183

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
3642 ESCALATE, IRAS 1007183

Study information

Scientific Title
ESCALATion of medical therapy following multimodality plaque Evaluation in high-risk Chronic Coronary Syndromes

Acronym
ESCALATE

Study objectives
Primary objectives:
To characterise the impact of systemic anti-inflammatory therapy with colchicine on features of non-flow limiting coronary plaque using multi-modality intracoronary imaging.

Secondary objectives:
1. To assess the impact colchicine on microvascular function in patients with chronic coronary syndrome and high clinical risk
2. To assess the impact of colchicine therapy on circulating leukocyte function and protein expression and correlate to changes in coronary plaque morphological characteristics

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/04/2024, East Midlands - Leicester Central Research Ethics Committee (2 Redman Place, London, E20 1JQ, United Kingdom; +44 (0)207 104 8066, +44 (0)207 104 8227, +44 (0)207 104 8284; leicestercentral.rec@hra.nhs.uk), ref: 24/EM/0082

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Chronic inflammation; atherosclerosis; coronary artery disease; chronic coronary syndromes

Interventions
Patients with coronary artery disease, high clinical risk and evidence of residual systemic inflammation despite established statin therapy will be eligible for recruitment. All eligible patients will undergo invasive intracoronary assessment, to identify those with non-flow limiting lesions, and high-risk features on intracoronary imaging.

Using an online web-based system, patients will undergo 1:1 randomisation with alternating blocks of 2 and 4. This will be an open-label study. Those randomised to the intervention arm will receive once daily 0.5 mg oral colchicine, in addition to usual care. The control arm will involve usual care only. Patients will be followed up for 6 months.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Colchicine

Primary outcome(s)
Minimal fibrous cap thickness in a defined arterial region of interest, as assessed by intracoronary optical coherence tomography (OCT) at baseline and 6 months

Key secondary outcome(s))
Secondary clinical and safety endpoints:
1. Major adverse cardiovascular event (MACE): Composite of cardiovascular death, non-fatal myocardial infarction, unplanned revascularisation and ischaemic stroke
2. All-cause mortality (i.e., number of deaths of any cause)
3. Cardiovascular death (i.e., number of deaths attributable as 'Cardiovascular death')
4. Non-fatal myocardial infarction
5. Unplanned revascularisation
6. Ischaemic stroke
7. Acute kidney injury
8. Major bleeding events (BARC [Bleeding Academic Research Consortium] 3-5)
9. Hospitalisation with heart failure
10. Hospitalisation with serious infection
11. Patient-reported angina, as assessed by Canadian Cardiovascular Society (CCS) Angina Grade
All clinical and safety endpoints will be assessed with an in-person clinical review of the patient at hospital discharge, 3 and 6 months.

Secondary intracoronary imaging endpoints:
All intracoronary imaging endpoints will be assessed with intracoronary OCT or intracoronary near-infrared spectroscopy intravascular ultrasound (NIRS-IVUS) at baseline and 6 months:
12. Percentage change in minimal fibrous cap thickness, as determined by OCT, in a defined arterial region of interest
13. Absolute (°) and relative (%) change in lipid arc, as determined by OCT, in a defined arterial region of interest
14. Percentage change in lipid index, as determined by OCT, in a defined arterial region of interest
15. Absolute (°) and relative (%) change in maximal macrophage arc, as determined by OCT, in a defined arterial region of interest
16. Absolute change in maximum lipid core burden index in a 4-mm segment (maxLCBI4mm), as determined by NIRS, in a defined arterial region of interest
17. Relative change (%) in maximum lipid core burden index in a 4-mm segment (maxLCBI4mm), as determined by NIRS, in a defined arterial region of interest
18. Absolute change in lipid core burden index (LCBItotal), as determined by NIRS, in a defined arterial region of interest
19. Change in percent atheroma volume, as determined by IVUS, in a defined arterial region of interest
20. Change in maximal plaque burden, as determined by IVUS, in a defined arterial region of interest

Secondary invasive haemodynamic endpoints:
All invasive haemodynamic indices will be recorded at baseline and 6 months, using an intracoronary pressure/thermistor tipped wire:
21. Absolute and percentage change in coronary flow reserve (CFR), measured in artery of interest
22. Absolute and percentage change in index of microvascular resistance (IMR), measured in artery of interest
23. Absolute and percentage change in vessel fractional flow reserve (FFR), measured in artery of interest

Secondary biomarker endpoints:
Biomarker analysis will be performed using blood samples at baseline and 6 months:
24. High sensitivity troponin at 6 months and change from baseline
25. NT-pro BNP level at 6 months and change from baseline
26. High-sensitivity c-reactive protein (hs-CRP) at 6 months and change from baseline

Leukocyte function sub-study:
27. Cytokine profile of isolated circulating neutrophils and peripheral blood mononuclear cells (PBMCs) following stimulation with oxidised-LDL, at 6 months and change from baseline
28. Surface proteomic analysis of isolated circulating neutrophils and PBMCs, at 6 months and change from baseline

Completion date
07/10/2025

Eligibility

Key inclusion criteria
1. Ability to provide written informed consent
2. Age 18 to 90 years old
3. Male, or female of non-child-bearing potential
4. Elevated clinical risk, as evidenced by ≥1 of:
4.1. Previous spontaneous acute myocardial infarction (diagnosed according to the universal MI criteria) with or without persistent ST-segment elevation
4.2. Previous stroke or intervention for peripheral arterial disease (i.e., evidence of atherosclerotic disease affecting >1 vascular bed)
4.3. Established diagnosis of diabetes mellitus
4.4. Systemic Coronary Risk Estimation 2 (SCORE2) or Systemic Coronary Risk Estimation 2 – Older Persons (SCORE2-OP) algorithm 10-year risk of fatal and non-fatal myocardial infarction or stroke >10%
5. Documented evidence of coronary artery disease, with an angiographically moderate stenosis on invasive coronary angiography (30-80%)
6. At least one non-flow limiting (FFR >0.80) moderate lesion with TCFA (minimum fibrous cap thickness of <120μm and lipid arc >90°)
7. History of prescribed statin therapy, at a stable dose, for >4 weeks
8. Evidence of residual inflammation at baseline (i.e., high-sensitivity CRP ≥2)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
90 years

Sex
All

Key exclusion criteria
1. Women who are pregnant, breastfeeding, or of child-bearing potential
2. Symptoms of unstable angina, characterised as: angina at rest; new onset of severe exertional angina (CCS grade III or higher for <4 weeks); or distinct, sudden, intensification of previously stable angina
3. Previous spontaneous acute myocardial infarction (diagnosed according to the universal MI criteria) with or without persistent ST-segment elevation <4 weeks from recruitment
4. Previous coronary artery bypass grafting
5. Known chronic total occlusion of coronary artery
6. Chronic kidney disease with eGFR <50 mL/min/1.73 m2 per MDRD formula or renal replacement therapy at baseline assessment
7. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C, or confirmed ALT/AST levels > 3 times ULN or total bilirubin > 2 times ULN) at baseline assessment
8. Symptoms of severe heart failure (systolic or diastolic) with New York Heart Association (NYHA) Functional Classification 3 or 4
9. Moderate or severe valvular heart disease considered likely to require intervention
10. History of blood dyscrasia including anaemia, thrombocytopenia, neutrophilia, leukopenia or other abnormality of blood count at baseline
11. Peripheral neuritis, myositis or marked myo-sensitivity to statins
12. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
13. Patients with suspected or proven immunocompromised state, including:
13.1. Those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded
13.2. Those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy
14. History of hypersensitivity to the study drug or its constituents
15. Patients who have received an investigational drug or device within 30 days (inclusive) of baseline assessment, or who are expected to participate in any other investigational drug or device study during the conduct of this trial
16. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
17. Established long-term pharmacotherapy with a strong CYP3A4 inhibitor or a P-glycoprotein inhibitor (P-gp) (e.g., macrolide antibiotics, ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, verapamil, diltiazem and disulfiram)
18. Contraindications to intravenous adenosine will exclude patients from adenosine induced hyperaemia

19. Any life-threatening condition with life expectancy <6 months that might prevent the patient from completing the study.

Date of first enrolment
04/06/2024

Date of final enrolment
01/06/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Kings College Hospital
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Sponsor information

Organisation
King's College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Charity

Funder Name
King's College Hospital NHS Foundation Trust - Cardiac Research Charity

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Not expected to be made available