Trained immunity by dual-pathway inhibition (low-dose rivaroxaban and acetylsalicylic acid) in coronary artery disease

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To demonstrate elevation in immune responsiveness to LPS stimulation when switching from ASA to DPI in patients with CAD, and to further explore whether changes in monocyte function and epigenetic landscape are responsible for the observed...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON50625

Source
ToetsingOnline

Brief title
DUALCAD

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerotic heart disease, coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Coronary artery disease, Dual-pathway inhibition, Rivaroxaban, Trained immunity

Outcome measures

Primary outcome

The primary outcome is a change in whole blood immune responsiveness to LPS stimulation when switching from ASA to DPI.

Secondary outcome

Secondary outcomes are changes in white blood cell count and distribution, change in monocyte immune responsiveness to LPS stimulation, change in enrichment of epigenetic marks on genes associated with inflammation in monocytes, and changes in circulating cytokines when switching from ASA to DPI.

Study description

Background summary

Coronary artery disease (CAD) is a manifestation of systemic atherosclerosis for which single antiplatelet therapy (SAPT) is indicated if patients are stable. Recently dual pathway inhibition (DPI) by combining a low-dose factor Xa inhibitor (rivaroxaban 2.5mg twice daily) with a single platelet inhibitor (ASA) has been demonstrated to be beneficial in treating CAD. The exact mechanisms underlying the benefits of DPI, are not completely understood. CAD is characterised by a state of chronic low-grade inflammation, where monocytes from CAD patients have a higher immune responsiveness to ex vivo stimulation with lipopolysaccharide (LPS) compared to healthy matched controls. Surprisingly, we have recently observed an elevation in ex vivo immune responsiveness to LPS stimulation when switching from ASA monotherapy to DPI of ASA combined with rivaroxaban in patients with peripheral arterial disease (n=11; unpublished). Remarkably this was associated with no changes in systemic inflammation, as determined by Olink proteomics analysis. These findings suggest that factor Xa inhibitors can enhance immune cell responsiveness despite being clinically beneficial to CAD. The exact mechanisms contributing

to the observed increased immune responsiveness remain unexplored.

Study objective

To demonstrate elevation in immune responsiveness to LPS stimulation when switching from ASA to DPI in patients with CAD, and to further explore whether changes in monocyte function and epigenetic landscape are responsible for the observed elevations in immune responsiveness to LPS stimulation when treating with DPI.

Study design

An explorative clinical cohort study.

Intervention

patients will be prescribed rivaroxaban 2.5mg twice daily in addition to ASA 75-100mg once daily for a period of 12 weeks. Blood samples will be taken at baseline, and 4 and 12 weeks after switching ASA to DPI. The comparator is ASA monotherapy (baseline).

Study burden and risks

The use of DPI by low-dose rivaroxaban with ASA has been approved for various indications, such as coronary artery disease. DPI has shown to reduce ischemic events at the expense of more non-fatal bleedings, with a net-clinical benefit for DPI over ASA monotherapy.[5] Investigating the influence of adding rivaroxaban to ASA monotherapy on changes in immune responsiveness, white blood cell counts, monocytes and epigenetic landscape will facilitate understanding the mechanism underlying the benefits of DPI over ASA in CAD. Understanding this mechanism will facilitate optimizing treatment of future patients and prevent progression of the disease.
The risks include possible side effects of rivaroxaban (2.5 mg), such as bleedings, muscle pain, stomach and bowel complaints, dizziness, headache, skin rash, and malaise. To minimize risk, the research team will evaluate the subject for any adverse events related to the treatment during the course of the study.
The total period of DPI treatment has been set on 12 weeks, since an elevation in immune responsiveness to LPS stimulation when switching ASA to DPI has been observed after 12 weeks of DPI treatment in patients with peripheral arterial disease. Therefore, this time frame should be sufficient to answer our research questions. The additional measurement after 4 weeks will inform us about an eventually course of rivaroxaban influencing changes in immune responsiveness, white blood cell counts, monocytes and epigenetic landscape. Additionally, when similar results are found after 4 and 12 weeks of DPI, there are substantiated arguments that participants in future studies on comparable topics can be

exposed to a shorter treatment period.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Stable CAD
- with an indication for single antiplatelet therapy according to international (ESC) guidelines,
- at least16 years old
- Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Use of more intensive antithrombotic treatment (dual antiplatelet therapy, dual-pathway inhibition, direct oral anticoagulants, vitamin k antagonists)
- Contra-indication to rivaroxaban
o Hypersensitivity to rivaroxaban
o at significant risk for major bleeding
* current gastrointestinal ulceration
* presence of malignant neoplasms, with the exception of non-melanoma skin cancer
* recent (<2 months) brain or spinal injury
* recent (<3 months) brain or spinal surgery
* recent (<3 months) intracranial, gastrointestinal or pulmonary hemorrhage
* presence of arteriovenous malformations,
* major intraspinal or intracerebral vascular abnormalities
* congenital or acquired bleeding disorders
* uncontrolled severe arterial hypertension (180 mmHg or more systolic, or 110 mmHg or more diastolic)
o Severe hepatic disease: Child Pugh B or C
o Severe kidney failure: estimated glomerular filtration rate <15 ml/min or requiring dialysis
o severe heart failure with known ejection fraction < 30% or New York Heart Association class III or IV symptoms
o concomitant treatment with medication with a strong pharmacokinetic interaction with rivaroxaban, leading to contra-indication according to the *regionale_NOAC_richtlijn* [11]
- Pregnant or breastfeeding women
- Unable to give informed consent

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-03-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspirin
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xarelto
Generic name:	Rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-006189-19-NL
CCMO	NL79727.091.21

Study results

Date completed: 11-07-2022

Actual enrolment: 20

Summary results
Trial is onging in other countries