Low INR to Minimize bleeding with mechanical valves Trial

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON56927

Source
ToetsingOnline

Brief title
LIMIT

Condition

- Cardiac valve disorders

Synonym
bleeding post-mechanical valve replacement; thromboembolism post-mechanical valve replacement.

Research involving
Human

Sponsors and support

Primary sponsor: Population Health Research Institute
Source(s) of monetary or material Support: Canadian Institute of Health Research

Intervention

Keyword: INR Target Range, Mechanical Valves, Oral Vitamin K antagonist

Outcome measures

Primary outcome

The primary outcome is the incidence of major bleeding.

Secondary outcome

The most important secondary outcome is all thrombosis/thromboembolism (composite of ischemic stroke, systemic thromboembolism, valve thrombosis).

Other secondary outcomes include:

1) All-cause mortality (selected rather than cardiovascular mortality, as cause-specific mortality is often difficult to ascertain or define in complex cardiovascular patients in whom multi-end-organ dysfunction may accompany cardiovascular decline)

2) All bleeding

3) Minor bleeding

4) All stroke

5) Ischemic stroke

6) Hemorrhagic stroke

7) Type 1, 2 or 3 myocardial infarction

8) Systemic thromboembolism

9) Valve thrombosis

10) Pulmonary embolism

11) Deep vein thrombosis

12) New renal replacement therapy

13) Time in therapeutic range

14) Proportion of patients with extreme INR values (>4)

Study description

Background summary

A vitamin K antagonist is a blood thinner used to prevent blood clot formation in patients with mechanical heart valves. Blood clots can block blood flow to the brain, heart, or other parts of the body. Mechanical heart valves increase the risk of blood clots so patients with a mechanical heart valve must take a vitamin K antagonist to reduce their risk of stroke and other blood clot-related problems.

The degree to which a vitamin K antagonists 'works' varies from person to person, and so dosage is determined by measuring each person's response to the drug as an 'international normalized ratio' or INR. A patient with an INR over 1.0 has blood that takes longer to clot than average, and increasing INR values represent increasing time required for blood to clot. While an INR over 1.0 decreases clotting risk, it also increases bleeding risk. It is important to carefully balance these risks. Specific INR targets are recommended for patients with a mechanical heart valve, but these recommendations differ between scientific groups and are based on low quality evidence. Recent studies suggest that a lower INR target range than is currently recommended can be used safely. A laboratory study showed that warfarin effectively prevents blood clot formation on mechanical heart valves as long as the INR is 1.5 or above. Two moderately-sized clinical studies showed that an INR target range of 1.5-2.5 resulted in less bleeding than the usual higher target range without increasing blood clot formation or stroke in patients with a newer valve model. Whether we could use a lower INR target range for patients with a mechanical aortic valve remains controversial.

The purpose of this research is to find out if a lower INR target range (1.5 to 2.5) results in lower rates of bleeding when compared to the current guideline recommended INR target, in patients with mechanical valves. The study will also confirm that a lower target INR maintains adequate protection against blood clots.

Study objective

The objective in the vanguard phase of the LIMIT trial is to assess the feasibility of recruiting 400 subjects over approximately 3 years at 5 centres. The objectives in the full trial are to evaluate the safety and efficacy of a

common, lower INR target range in patients with bileaflet aortic mechanical valves

Study design

The LIMIT trial is a prospective, randomized, open-label, blinded end-point, multicenter clinical trial.

Intervention

All enrolled patients will already be taking a VKA according to typical care. The intervention group will receive a dose titrated to achieve an INR target of 1.5 to 2.5. The control group will receive a dose titrated to achieve the current guideline recommended INR range. Oral VKA dosage and INR frequency monitoring will be under the direction of the local anticoagulation clinic. We will mandate at least 10 INR measurements per year or at minimum (a 6 week specific dosing algorithm or INR monitoring schedule).

Study burden and risks

For patients who are allocated to the lower INR target range, the risk of developing a blood clot may be increased. Blood clots may dislodge from the site they develop and travel to other parts of the body, where they have the potential to block blood flow and cause stroke, heart attack, or gut or limb ischemia. However, based on previous studies that observed no increased risk of blood clot formation in patients assigned to a lower INR target range, we believe this risk is very small.

Patients may or may not benefit directly from participating in this study. If their INR target range is lowered as part of the study, it may reduce the risk of bleeding.

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

1) Have had a bileaflet mechanical heart valve implant in the aortic position >=3 months ago,
2) Be >=18 years of age at the time of enrolment,
3) Provide written informed consent (either from the patient or a substitute decision-maker).

Exclusion criteria

1) Have a second implanted mechanical valve (any position),
2) Lower boundary of planned INR range is less than 2.0,
3) Pregnant or expecting to become pregnant during the study follow-up.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-12-2023
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	acenocoumarol
Generic name:	acenocoumarol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fenprocoumon Sandoz
Generic name:	Fenprocoumon Sandoz
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	13-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2019-004975-37-NL
ClinicalTrials.gov	NCT036362
CCMO	NL78645.078.21