



Low INR to Minimize bleeding with mechanical valves Trial (LIMIT)

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Background

- Mechanical valves are recommended for young adults with severe valvular disease
 - However, they require lifelong anticoagulation therapy
- Current guidelines recommend a **INR target of 2.0-3.0** in patients with mechanical bileaflet heart valves in the aortic position in the absence of additional risk factors, but they recommend an **INR target of 2.5-3.5** in those with additional risk factors
 - Based on low quality observational evidence
- The results of several recent RCTs suggest that a lower INR target for mechanical valves in the aortic position are safer
 - Lower INR targets may decrease the risk of bleeding
 - Lower INR targets have similar thromboembolic risk
- Therefore, the optimal INR target remains unclear

Research Question

Full trial: In adult patients (≥ 18 years) with a bileaflet aortic mechanical valve, is a low INR target (INR 1.5-2.5) non-inferior to current target INR recommended by guidelines with respect to thrombosis/thromboembolism and superior with respect to major bleeding?

Trial Design

- A prospective, randomized, open-label, blinded end-point (PROBE), multicenter clinical trial. The intervention of interest is a low INR target range (1.5 to 2.5) compared to the current practice as per guideline recommendations
- **Full trial:** 2625 patients to be recruited into the full trial at 30-50 centres internationally

Patient Population

Inclusion Criteria

1. Age \geq 18 years
2. Is greater than 3 months post mechanical bileaflet aortic valve replacement
3. Written informed consent from either the patient or substitute decision maker

Exclusion Criteria

1. Has 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

Primary Outcomes

The primary outcomes of the **Full trial** are thrombosis/thromboembolism (composite of ischemic stroke, systemic thromboembolism and valve thrombosis) and major bleeding.

Secondary Outcomes

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 clinically important 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)

Patient follow-up

