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

Vanguard phase: Is it feasible to conduct a large trial evaluating the safety and efficacy of a lower INR target range (1.5-2.5) in patients with bileaflet mechanical valves?

Full trial: In adult patients (≥18 years) with an aortic mechanical valve, is a low INR target (INR 1.5-2.5) superior to target the INR in the range recommended by current guidelines with respect to major bleeding (primary outcome)?

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

- ***Vanguard phase***: approximately a 3-year, 400 patient feasibility trial, used to assess whether the LIMIT protocol is feasible to proceed to a full, international, multi-centre RCT

- ***Full trial*****:** 2660 patients to be recruited into the full trial at 10-20 centres internationally

Patient Population

Inclusion Criteria

1. Age ≥ 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 outcome of the **Vanguard phase** is the feasibility of a large-scale trial as defined by the ability to recruit 400 patients over 3 years

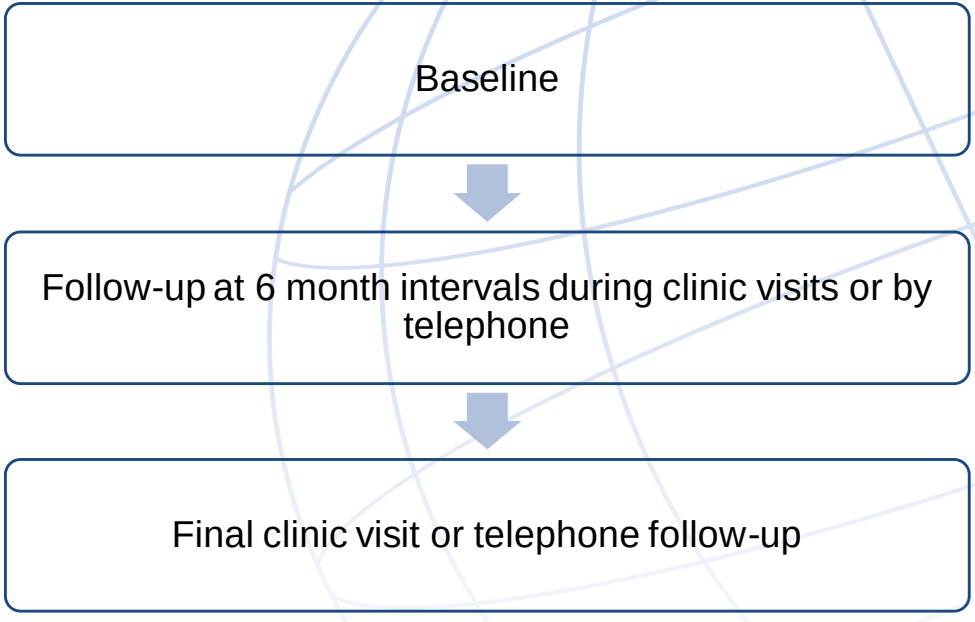
The primary outcome of the **Full trial** is the incidence of major bleeding

Secondary Outcomes

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)

Patient follow-up



The final visit will be determined once 120 primary outcome events have occurred