Anticoagulation Bridging

The NHLBI-sponsored trial

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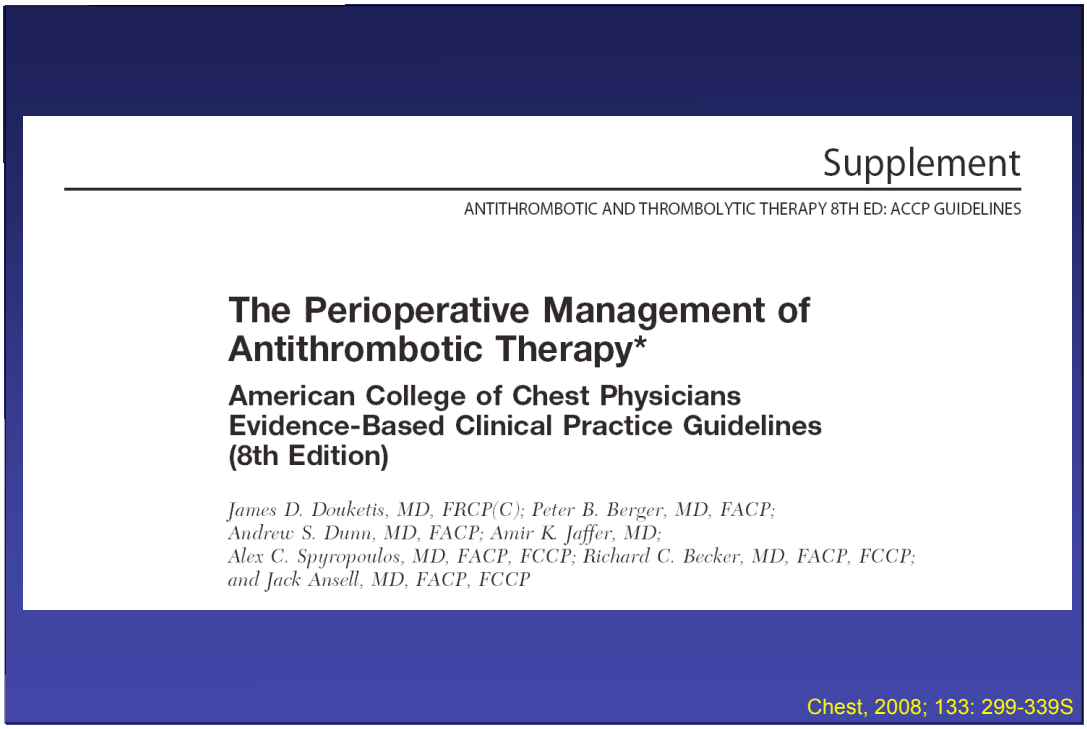
Disclosures

- NHLBI – funding for the BRIDGE trial.
- Eisai – provision of dalteparin for use in the trial.



Perioperative Management of Anticoagulant Therapy

- Approximately 250,000 patients on chronic anticoagulant therapy are assessed annually for perioperative management in North America.
- The majority of these patients are receiving anticoagulation for atrial fibrillation or a mechanical heart valve.

Perioperative Management

- Two principal issues to be addressed for each patient on chronic anticoagulation who needs to undergo a surgery or procedure:
  - Is interruption of antithrombotic therapy in the perioperative period needed?
  - If antithrombotic therapy is interrupted, is bridging anticoagulation necessary?

Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	• Prosthetic mitral valve. • Older aortic valve prostheses. • Recent CVA or TIA.	• $CHADS_2$ score of 5-6. • Recent CVA or TIA • Rheumatic heart valve disease.	• Recent VTE (≤ 3 mos). • "Severe" thrombo-philia (*e.g.*, APS, AT deficiency).

Chest, 2008; 133: 299-339S

Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Mechanical Heart Valve	Atrial Fibrillation	VTE
Moderate	• Bileaflet prosthetic aortic valve and: AF; prior CVA or TIA; HTN; DM; CHF; and/or age >75 yrs.	• $CHADS_2$ score of 3-4.	• VTE within 3-12 months. • "Nonsevere" thrombophilia. • Recurrent VTE. • Active cancer.

Chest, 2008; 133: 299-339S

Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Mechanical Heart Valve	Atrial Fibrillation	VTE
Low	• Bileaflet prosthetic aortic valve without AF or other CVA risk factors.	• $CHADS_2$ score of 0-2. • No prior CVA or TIA.	• Single VTE occurring > 12 months ago and no VTE risk factors.

Chest, 2008; 133: 299-339S

Hemorrhagic Risks Associated with Bridging Therapy

- In a meta-analysis of 1903 patients who had bridging therapy while warfarin was interrupted, the incidence of major bleeding was 2.3% (95% CI, 1.7-3.3%).
- In a systematic review, major bleeding associated with a variety of bridging strategies was 2.9% (CI, 2.3-3.7%).

Kaatz et al, J Thromb Haemost, 2007; 5: O-T-049.
Spyropoulos & Turpie, Curr Opin Pulm Med, 2005; 11: 373-9.

Rationale for a Study of Bridging Therapy

- Multiple observational studies have assessed bridging therapy, but these studies provide the weakest level of evidence (Level 2C) to guide clinical decision-making.
- No prospective, randomized studies assessing the efficacy and safety of bridging therapy exist.
- Guidelines from the ACCP and joint guidelines from the AHA and ACC are inconsistent.

Why do a bridging study with atrial fibrillation patients?

- Represents the largest population of individuals on anticoagulant therapy.
- Survey data indicates that clinical equipoise exists in this population of patients.
- Patients with prosthetic heart valves and VTE are more frequently considered 'higher risk'.
- Outcome measures can be more standard.
- Bleeding outcomes can apply to other groups.

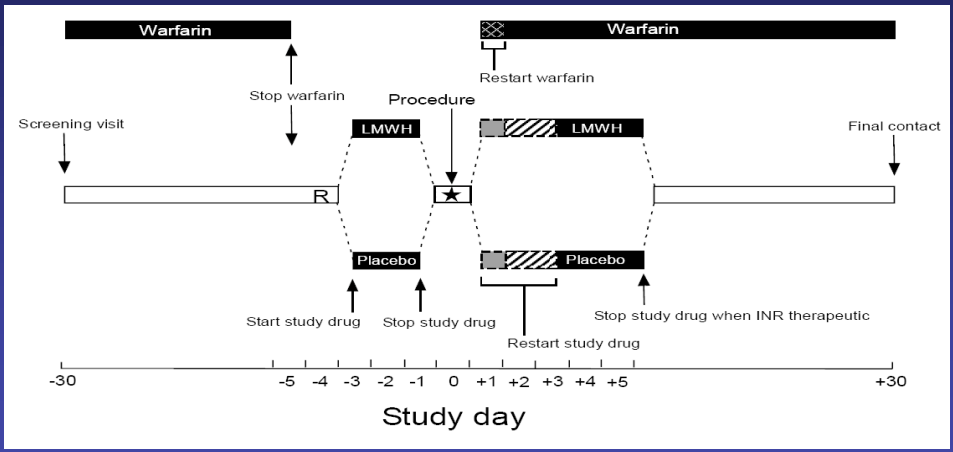
*B*ridging Anticoagulation in Patients who *R*equire Temporary *I*nterruption of Warfarin Therapy for an Elective Invasive Proce*D*ure or Sur*GE*ry

"BRIDGE"

BRIDGE: Study Objectives

- To compare the *efficacy* of bridging anticoagulation (therapeutic-dose LMWH) with no bridging anticoagulation (placebo) on the rate of arterial thromboembolism in patients with atrial fibrillation who require temporary interruption of warfarin.
- To compare the *safety* of bridging anticoagulation with no bridging anticoagulation on the rate of major bleeding in patients who require temporary interruption of warfarin.

BRIDGE: Study Design



Study Population

- Inclusion Criteria (1)
  - –Adult Male or female, age 18 years or older.
  - –Receiving warfarin therapy (for at least 3 months), administered to achieve an INR range of 2.0-3.0.
  - –Require temporary interruption of warfarin for pre-specified elective surgery or procedure.
  - –Have at least one of the following conditions: (a) chronic (permanent or paroxysmal) nonvalvular atrial fibrillation, confirmed by prior ECG recording or pacemaker/ACD interrogation; or (b) chronic (permanent or paroxysmal) valvular atrial fibrillation with evidence of mitral valve disease.

Study Population

- Inclusion Criteria (2)
  - –Have at least one of the following major stroke risk factors:
    - Age > 75 years.
    - Hypertension.
    - Diabetes mellitus.
    - Congestive heart failure or left ventricular dysfunction.
    - Previous ischemic stroke, systemic embolism, or TIA.

Study Population

- Exclusion criteria (1)
  - Any mechanical prosthetic heart valve.
  - Stroke (ischemic or hemorrhagic), systemic embolism or TIA within past 12 weeks.
  - Venous thromboembolism within the past 12 weeks.
  - Major bleeding within the past 6 weeks.
  - Severe renal insufficiency (calculated creatinine clearance less than 30 mL/min).
  - Thrombocytopenia (platelet count < 100 x 10^9/L)
  - Life expectancy less than one month.
  - Pregnancy.

Study Population

- Exclusion criteria (2)
  - Any condition that impairs compliance with trial protocol.
  - Allergy to heparin or history of HIT.
  - Any of the following surgeries: (a) cardiac surgery; (b) intracranial or intraspinal neurosurgery; or (c) high-risk non surgical procedures (e.g., brain biopsy).
  - Other surgical or non-surgical procedure deemed by the surgeon or proceduralist to preclude LMWH in the postoperative setting.
  - More than one surgery during the trial period.
  - Prior participation in this trial.
  - Inability or unwillingness to provide informed consent.

Types of Surgeries or Procedures

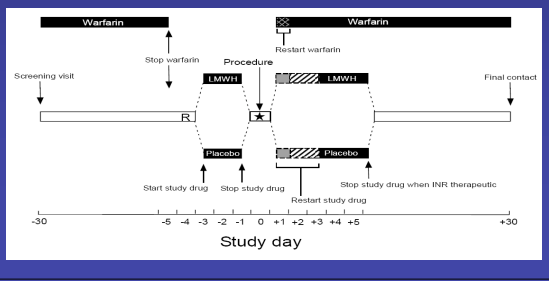
- *Minor* surgeries or procedures include:
  - Gastrointestinal endoscopy (with or without biopsy).
  - Cardiac catheterization (with or without percutaneous coronary intervention.
  - Dental surgery or other dental procedure.
  - Dermatologic surgery or other dermatologic procedure.
  - Cataract removal or other ophthalmologic procedure.
  - Any other surgery or procedure lasting less than 1 hour.

Types of Surgeries or Procedures

- *Major* surgeries or procedures include:
  - Intra-abdominal surgery (e.g., bowel resection).
  - Intra-thoracic surgery (e.g., lung resection).
  - Major orthopedic surgery (e.g., hip or knee replacement).
  - Peripheral arterial revascularization (e.g., AAA repair; vascular bypass procedure).
  - Urologic surgery (e.g., prostatectomy, bladder tumor resection).
  - Permanent pacemaker or internal defibrillator insertion.
  - Major procedure (e.g., colonic polyp resection, renal biopsy).
  - Any other surgery or procedure lasting more than 1 hour.

BRIDGE: Overview of Activities

- Recruitment: between Day -30 and Day -5.
- Randomization: between Day -14 and Day -5, to LMWH or Placebo.
- Follow-up: through Day +30 (up to +37) after the surgery or procedure.



Primary Efficacy Endpoints

- Ischemic stroke.
  - Symptoms > 24 hr, or symptoms of any duration with evidence for infarction on CT or MRI.
- Transient ischemic attack.
  - Symptoms < 24 hr, with resolution, and no evidence for infarction on CT or MRI.
- Systemic embolism.
  - Symptoms affecting limb(s) or abdominal organs, with intraoperative or imaging confirmation.

Primary Safety Endpoints

- Symptomatic or clinically-overt bleeding that is associated with one or more of:
  - Transfusion of ≥ 2 units heterologous pRBC;
  - Decrease in hemoglobin level >2 gm/dL (>20 gm/L);
  - Need for re-operation or invasive intervention (e.g., evacuation of a wound hematoma).
- Symptomatic or clinically-overt bleeding at a critical anatomic site.
- Fatal bleeding.

Secondary Efficacy Outcomes

- Acute myocardial infarction (ST- and non-ST-elevation.
- Symptomatic deep vein thrombosis confirmed by venous ultrasound or venography.
- Symptomatic pulmonary embolism confirmed by ventilation-perfusion lung scan, CT angiography, or pulmonary arteriography.
- Death.

Sample Size

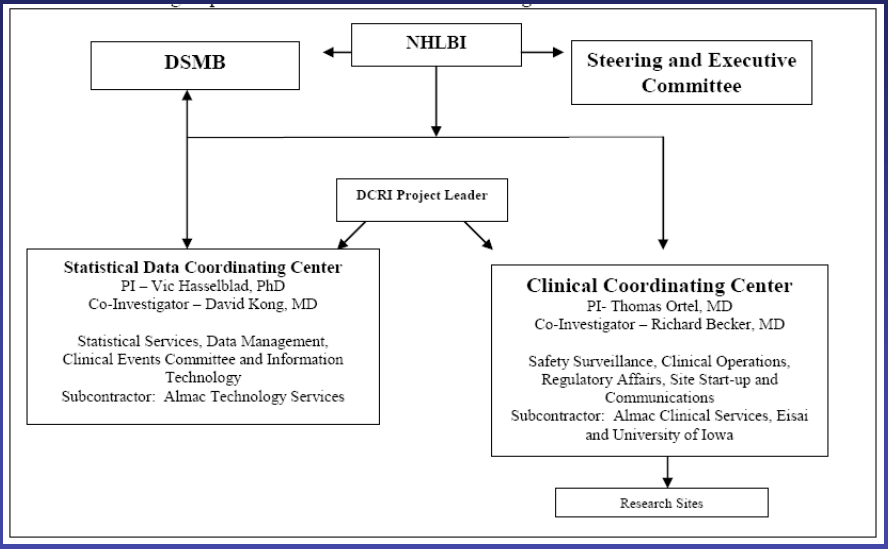
- Sample size estimates are based on the following assumptions:
  - Incidence of arterial thromboembolism in the bridging group = 1.0% (derived from systematic reviews of patients who received bridging).
  - Incidence of arterial thromboembolism in the "no bridging" group = 1.0% (derived from linked administrative database and cohort studies).
  - Non-inferiority margin = 1.0%.

Sample Size

- Estimate based on a non-inferiority margin of 1.0%, power of 80%, and a 2-tailed alpha of 0.05.

	Non-inferiority margin			
ATE in LMWH arm	0.5%	*1.0%*	1.5%	2.0%
0.5%	3308	927	465	307
1.0%	6317	*1641*	772	454
1.5%	9344	2375	1088	625
2.0%	12373	3127	1412	814

BRIDGE Operational Structure



BRIDGE Research Sites

- Target 45 research sites located in North America (US and Canada).
- Target enrollment at each site is projected at 2-3 patients per month.
- Enrollment is projected to be completed 44 months after initiation.
- As of 24 September 2009: 10 sites open (9 US, 1 Canadian), 6 patients recruited.

Questions?

Akashi Kaikyo Bridge, Japan
Central span: 1,991 m (6,532 ft)

BRIDGE