The Pendulum of Bridging Periprocedural Anticoagulant Therapy

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Disclosures

• Department of Veterans Affairs

• Industry Relationships:
  • Roche Diagnostics
  • Boehringer-Ingelheim
  • Bristol-Myers Squibb
  • Janssen Pharmaceuticals
  • Daiichi Sankyo
  • POC-INR device manufacturers
Outline

- Historical perspective
- Where are we at – evidence
- Where are we at – practical considerations
- Where do we need to go
Sixth ACCP Consensus Conference on Antithrombotic Therapy

March 12 - 14, 2000
Tucson, Arizona

Published as supplement to CHEST Volume 119/Number 1 (Suppl) January 2001
Bridging Therapy

» Management of oral anticoagulation for invasive procedures

» “Bridging” the time span between the withdrawal of warfarin and the return of normal coagulation status

...and / or

» “Bridging” the time between the initiation / resumption of warfarin and development of stable anticoagulation
Figure 3. Periprocedural Antithrombotic Strategies

Warfarin interruption produces an anticoagulation gap (A). Various strategies (C to K) attempt to emulate a theoretical ideal bridge (B).

Stephen J. Rechenmacher, James C. Fang
Journal of the American College of Cardiology, Volume 66, Issue 12, 2015, 1392–1403
Underlying Challenge

Balancing

risk of bleeding from procedure if anticoagulation not stopped

Against

risk of thrombotic complications during the time that anticoagulation is stopped
Lateral-Flow Prostheses

Starr-Edwards
Smeloff-Cutter
DeBakey-Surgitool
Kay-Shiley
Beall-Surgitool
Cooley-Bloodwell-Cutter
Annualized Thrombotic Rates by Valve Type and Position in the Absence of Anticoagulation

- Aortic St. Jude (65) 12.3%
- Mitral St. Jude (10) 22.2%
- Multiple St. Jude (3) 91%
- Bjork Shiley Aortic (27) 23%

ACCP 1995 Consensus Conference
Estimated Event Rates
Per 100,000 Patient Days

- Aortic St. Jude: 5.7*
- Mitral St. Jude: 29.7
- Aortic Bjork: 18.6
- Mitral Bjork: 36.9
- Aortic ball-cage: 27.6
- Mitral ball-cage: 71.4

Eckman, Pauker et al.
JAMA March 16, 1990
Cost Effectiveness of Hospitalization

First extra day of hospitalization
- $600,000 to $4,200,000 per TE event prevented
- $2,000,000 to $15,000,000 per death prevented

Second day
- $1.3 to $9.1 million per TE event prevented
- $4 to 34 million per death prevented

Third day
- $4 to 27 million per TE event prevented
- $13 to 100 million per death prevented

1990 dollars!!
By Eckman model, inpatient bridging, even for heart valves, with only one day of additional hospitalization, EIGHT times more costly per year of life saved than hemodialysis.

Cost effectiveness for lower thromboembolic risk indications, ie AF, even more costly.
2001
Definitive Benefit Studies
Prospective Demonstration Studies

- Johnson & Turpie, 112 patients
- Tinmouth, 27 patients
- Spandorfer, 20 patients
Bridging 2001 – 2012

2001
- Bridging generally involved high TE risk valves
- The only widely available option was inpatient UFH

2012
- AF became most common indication for anticoagulation
- Dual leaflet valves became predominant
- Outpatient bridging with LMWH
- Potential for benefit decreased due to decreased average risk, but utilization skyrocketed due to ease of LMWH

But was there a net benefit for patients?
Was medicine following “Primum Non Nocere”?
# 2017 Bridging Studies

<table>
<thead>
<tr>
<th>Study/First Author (Ref. #)</th>
<th>Year Published</th>
<th>Study Period</th>
<th>Study Type</th>
<th>Number of Studies</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn et al. (16)</td>
<td>2003</td>
<td>1966-2001</td>
<td>Systematic review</td>
<td>31</td>
<td>1,176</td>
</tr>
<tr>
<td>Siegal et al. (10)</td>
<td>2012</td>
<td>2001-2010</td>
<td>Meta-analysis</td>
<td>34</td>
<td>12,278</td>
</tr>
<tr>
<td>Steinberg et al. (2)</td>
<td>2015</td>
<td>2010-2011</td>
<td>Prospective cohort</td>
<td>1</td>
<td>2,280</td>
</tr>
<tr>
<td>Clark et al. (12)</td>
<td>2015</td>
<td>2006-2012</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>1,812</td>
</tr>
<tr>
<td>Cavalcanti et al. (14)</td>
<td>2015</td>
<td>2004-2012</td>
<td>Retrospective Cohort</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>RE-LY (28)</td>
<td>2015</td>
<td>2005-2008</td>
<td>Post-hoc subgroup analysis</td>
<td>1</td>
<td>4,106</td>
</tr>
<tr>
<td>BRIDGE (4)</td>
<td>2015</td>
<td>2009-2014</td>
<td>Randomized controlled trial</td>
<td>1</td>
<td>1,813</td>
</tr>
<tr>
<td>Combined†</td>
<td>2015</td>
<td>2001-2015</td>
<td>Review</td>
<td>39</td>
<td>22,334</td>
</tr>
</tbody>
</table>

Values are n or % unless otherwise indicated. *Denominator differs from number of cases stated (12,278) due to heterogeneity of defining currently relevant data.

RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etxilate.

J Am Coll Cardiol 2015;66:1392–403
In conclusion, we found that early after mechanical valve replacement, therapeutic dose bridging was associated with a similar risk of thromboembolic complications, but a 2.5 to 3-fold increased risk of major bleeding compared with prophylactic dose bridging.

Thrombosis and Hemostasis. 2014:112/6 (DEC) pp. 1077-1327
Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures

Original Investigation

Nathan P. Clark, PharmD; Daniel M. Witt, PharmD; Loren E. Davies, PharmD; Edward M. Saito, PharmD; Kathleen H. McCool, PharmD; James D. Douketis, MD; Kelli R. Metz, PharmD; Thomas Delate, PhD

CONCLUSIONS AND RELEVANCE Bridge therapy was associated with an increased risk of bleeding during warfarin therapy interruption for invasive procedures in patients receiving treatment for a history of VTE and is likely unnecessary for most of these patients. Further research is needed to identify patient- and procedure-related characteristics associated with a high risk of perioperative VTE recurrence during warfarin therapy interruption.

Overuse of Bridging Anticoagulation for Patients With Venous Thromboembolism

First, Do No Harm

Daniel J. Brotman, MD; Michael B. Streiff

JAMA Intern Med. 2015:175(7):1163-1168
CONCLUSIONS

In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT00786474.)
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation


N Engl J Med
Volume 373(9):823-833
August 27, 2015
BRIDGE Study Design.

Mean CHADS2: 2.3, 38.3% 3 or higher
CHADS2 of 5: 50
CHADS2 of 6: 8 patients
## Study Outcomes

**Table 3. Study Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01*, 0.73†</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.10†</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12.0)</td>
<td>187 (20.9)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

* P value for noninferiority.
† P value for superiority.

Conclusions

- In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.
Practical Approach to Bridging

REVIEW TOPIC OF THE WEEK

Bridging Anticoagulation
Primum Non Nocere

Stephen J. Rechenmacher, MD, James C. Fang, MD

J Am Coll Cardiol 2015;66:1392–403
Step 1:
What is the Bleeding Risk?

➤ What procedure is being considered?
➤ What is the risk of bleeding if the patient remains anticoagulated?
➤ What is the ability to identify and control bleeding should it occur?
➤ What is the potential for damage should bleeding occur?
**Low Bleeding Risk by Procedure**

**TABLE 2** Procedures Amenable to Uninterrupted Therapeutic Warfarin

<table>
<thead>
<tr>
<th>Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies</td>
</tr>
<tr>
<td>Endovascular interventions</td>
</tr>
<tr>
<td>Percutaneous coronary interventions</td>
</tr>
<tr>
<td>Cardiac electrophysiology studies and ablations</td>
</tr>
<tr>
<td>Cardiac device implantation (pacemakers, defibrillators, loop recorders)</td>
</tr>
<tr>
<td>Cataract surgery</td>
</tr>
<tr>
<td>Dermatologic surgery</td>
</tr>
<tr>
<td>Dental extractions</td>
</tr>
<tr>
<td>Epidural anesthetics and likely other interventional pain management techniques</td>
</tr>
<tr>
<td>Minor noncardiac surgeries</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
</tr>
<tr>
<td>Arthroscopic surgery</td>
</tr>
</tbody>
</table>
Step 2: What is the Thromboembolic Risk?

Estimated Annualized Thrombotic Risk (Stroke) in the **ABSENCE** of therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annualized Thrombotic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Lone” atrial fibrillation</td>
<td>1%</td>
</tr>
<tr>
<td>Average atrial fibrillation</td>
<td>5%</td>
</tr>
<tr>
<td>High risk atrial fibrillation</td>
<td>12%</td>
</tr>
<tr>
<td>Dual leaflet (St. Jude) aortic valve prosthesis</td>
<td>About 12%</td>
</tr>
<tr>
<td>Single leaflet (Bjork-Shiley) aortic valve prosthesis</td>
<td>About 20%</td>
</tr>
<tr>
<td>Dual leaflet (St. Jude) mitral valve prosthesis</td>
<td>About 20%</td>
</tr>
<tr>
<td>Multiple St. Jude prostheses</td>
<td>high</td>
</tr>
</tbody>
</table>
## Table 4: Bridging Recommendations and Considerations for High-Risk Patients by OAC Indication

<table>
<thead>
<tr>
<th>High-Risk OAC Indication</th>
<th>Thromboembolism Risk During OAC Interruption</th>
<th>Major Bleeding Risk</th>
<th>Guideline Recommendation (ACCP)</th>
<th>Guideline Recommendation (AHA/ACC/HRS)</th>
<th>Considerations Favoring Not Bridging</th>
</tr>
</thead>
</table>
| Atrial fibrillation (CHADS$_2$ ≥5) | +                                        | +++               | Bridging is favored (Grade 2C)   | No specific recommendation to bridge. Individualize based on bleeding and TE risk. | Short OAC interruption (<3–5 days)  
Concurrent dual antiplatelet therapy  
Active bleeding  
High risk of major bleeding (BleedMAP score)  
No prior TE  
Sinus rhythm |
| Recent VTE               | +                                        | ++                | Bridging is favored (Grade 2C)  | N/A                                    | Same as atrial fibrillation considerations  
VTE >3 months prior |
| Recent or active arterial TE | ++                                    | ++                | Bridging is favored (Grade 2C) | No specific recommendation to bridge. Individualize on the basis of bleeding and TE risk. | Same as atrial fibrillation considerations  
TE >3 months prior |
| Mechanical heart valve(s) | +++                                     | +++               | Bridging is favored (Grade 2C) | No specific recommendation to bridge. Individualize on the basis of bleeding and TE risk. | Same as atrial fibrillation considerations  
Aortic position only |

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AHA = American Heart Association; HRS = Heart Rhythm Society; OAC = oral anticoagulation; TE = thromboembolism; other abbreviations as in Table 1.
Bridging Therapy - Current Options

- IV UFH
- sc ufh (full dose)
- sc ufh (prophylactic dose)
- LMWH (full dose)
- LMWH (prophylactic dose)

With increased options at lower cost, threshold for treating is altered
Commercially Available LMWHs in the US

- **Enoxaparin**
  - 1 mg/kg/bid; 1.5 mg/kg/day
  - 30 mg bid, 40 mg bid

- **Dalteparin**
  - 100 IU/kg/bid; 120 IU/kg/bid; 200 IU/kg/day
  - 2500 IU q day; 5000 IU q day

- **Tinzaparin**
  - 175 IU/kg/day
Our recommendations relating to the need for bridging anticoagulation (section 2.4) will not refer to a specific bridging dose regimen and will deal with the issue of whether bridging is needed in a more generic sense.
Practical Considerations I

- **When to stop warfarin**
  - In general, 5 days pre-op
    - Current INR
    - Procedure related bleeding risk

- **When to start lmwh pre-op**
  - In general, 1-3 days pre-op
    - Current INR
    - Procedure related bleeding risk
    - Patient thromboembolic risk
Practical Considerations II

- **Treatment or prophylactic dose?**
  - Patient thromboembolic risk

- **When to give last dose lmwh pre-op?**
  - Generally at least 24 hours
    - Patient thromboembolic risk
    - Procedure related bleeding risk

- **When to resume warfarin?**
  - In general, day of procedure
Practical Considerations III

» When to resume lmwh?
   » In general, 12-24 hours post-op
   » Procedure related bleeding risk
   » Neurosurgical or closed procedures
   » Patient specific thromboembolic risk

» How often to check INR?

» How often to check platelets?
   » Concern of heparin induced thrombocytopenia
   » No clear consensus
   » Beware of time course if repeated exposure
Practical Considerations IV

- Who trains and monitors patients?
  - Anticoagulation service is ideal

- Which LMWH?
  - No data, all have been used

- What is maximal dose of LMWH?
  - Actual body weight vs. ideal vs. capped dose
    - Ongoing controversy, however, with limited duration of therapy, risk of accumulation limited

- What if renal impairment?
Questions to Resolve

- Which population DOES benefit?
- Which dose?
- Role of NOACS?
  - Probably NOT for mechanical valves.
Where are we headed?

PERIOP2

A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism

BRIDGE 2 - It depends on YOU!

Contact: thomas.ortel@duke.edu
The Periprocedural Bridging Pendulum

- 2000: High risk valves and inpatient unfractioned heparin
- Broadening of the indication to low-risk populations with lmwh
- 2017: Conduct of noninferiority trials to confirm the population that could benefit, not needed in most chronic VTE nor in AF CHADS2 of 4 or below.
- But, we are only half-way there …
BRIDGE 2 - It depends on YOU!
Contact: thomas.ortel@duke.edu