Lovenox Bridging – Who needs it? Practical Guidelines

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Tri–City Cardiology Consultants
Faculty Disclosure

I Have No Financial Interest to Disclose
The BRIDGE Trial: Relevant in 2013?

A Discussion of Recent Studies and New Oral Anticoagulant Options

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Potential Conflicts of Interest: J. Douketis

- None related to this topic
- Advisory Boards (Bayer, Bristol-Myers-Squibb, Astra-Zeneca, Boehringer-Ingelheim, Medicines Co.)
- Consultant (AGEN, Biotie, Ortho-Janssen, Boehringer-Ingelheim)

All funds derived from these sources deposited in university-based research accounts.
4 Reasons Why the BRIDGE Trial remains Relevant in 2013

1. Recent studies and clinical guidelines do not give us the answer that BRIDGE will provide

2. Recent studies, including randomized trial of bridging for pacemakers does not make BRIDGE less relevant

3. New oral anticoagulants (replacing warfarin) do not make BRIDGE less relevant…in fact, make BRIDGE more relevant!

4. Warfarin use will remain…so will the need to decide if bridging is needed!

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Why is this relevant to my practice?
Scope of the Clinical Problem

- Perioperative management of patients on VKA is common…
  315,000–1,275,000 patients/yr in North America need warfarin interruption (based on 2.5 million users)

- RE-LY study (warfarin vs. dabigatran for AF)
  26% of patients had at least 1 anticoagulant interruption during 2-yr follow-up

Healey JS, et al. Circulation 2012;126:343
Clinical Scenario No. 1

- 72-year old female with atrial fibrillation (AF) is receiving warfarin (target INR: 2.0–3.0)

- CHADS score = 3 (CHADSVASc = 5)
  - TIA one year ago
  - hypertension for 15 years

- Scheduled for elective colon resection for incidentally found colon cancer...
How to manage this patient’s anticoagulants?

1) stop warfarin 5 days pre–op, give *therapeutic–dose* bridging with LMWH (e.g. enoxaparin, 1 mg/kg BID) pre–op and post–op, first dose starting <24 hrs post–op

2) stop warfarin 5 days pre–op, give *therapeutic–dose* bridging with LMWH pre–op and post–op, first dose starting 48–72 hrs post–op

3) stop warfarin 5 days pre–op, administer *low–dose* LMWH (e.g. enoxaparin, 40 mg daily) pre– and post–op

4) stop warfarin 5 days pre–op and resume after procedure

What do the practice guidelines tell us?

Perioperative Management of Antithrombotic Therapy

James D. Douketis, MD, FCCP; Alex C. Spyropoulos, MD, FCCP; Frederick A. Spencer, MD; Michael Mayr, MD; Amir K. Jaffer, MD, FHM; Mark H. Eckman, MD; Andrew S. Dunn, MD; and Regina Kunz, MD, MSEpi

Chest 2012;141(Suppl):e326S–e350S
http://www.chestjournal.org

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## Thromboembolic Risk Stratification and Need for Bridging during Warfarin Interruption

<table>
<thead>
<tr>
<th>High Risk (consider bridging):</th>
<th>Moderate Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td><strong>Atrial fibrillation</strong></td>
</tr>
<tr>
<td>▸ recent (&lt;3 mos) stroke/TIA</td>
<td>▸ CHADS 3–4</td>
</tr>
<tr>
<td>▸ CHADS 5–6</td>
<td><strong>Mechanical heart valves</strong></td>
</tr>
<tr>
<td>▸ rheumatic heart</td>
<td>▸ bileaflet AVR + major risks</td>
</tr>
<tr>
<td><strong>Mechanical heart valve</strong></td>
<td><strong>VTE</strong></td>
</tr>
<tr>
<td>▸ caged-ball or tilting disc valve</td>
<td>▸ VTE within 3–12 months or cancer</td>
</tr>
<tr>
<td>▸ mitral valve</td>
<td></td>
</tr>
<tr>
<td>▸ recent (&lt;6 mos) stroke/TIA</td>
<td></td>
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<tr>
<td><strong>VTE</strong></td>
<td></td>
</tr>
<tr>
<td>▸ recent (&lt;3 mos) VTE</td>
<td></td>
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<tr>
<td>▸ severe thrombophilia (protein C, S or AT deficiency, APLA)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Risk (consider NO bridging):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td></td>
</tr>
<tr>
<td>▸ CHADS 0–2 (no prior stroke)</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical heart valves</strong></td>
<td></td>
</tr>
<tr>
<td>▸ bileaflet AVR without risks</td>
<td></td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td></td>
</tr>
<tr>
<td>▸ VTE &gt;12 months ago</td>
<td></td>
</tr>
</tbody>
</table>
Patients on Warfarin who need a Surgery or Procedure: Bridging or No Bridging?

- **Recommendation:** In patients with a MHV or AF or VTE at low risk for thromboembolism, we suggest low-dose SC LMWH or no bridging instead of bridging with therapeutic-dose SC LMWH or IV UFH. (Grade 2C)

- **Recommendation:** In patients with a MHV or AF or VTE at high risk for TE, we suggest bridging with therapeutic-dose SC LMWH instead of no bridging. (Grade 2C)
ACCP Grades of Recommendations

**Highest**

1A: strong recommendation based on high-quality evidence, “applicable to most patients in most circumstances”

1B

1C

2A

2B

2C: very weak recommendation based on very low quality evidence, “other alternative treatments may be equally reasonable…higher quality research likely to have major impact”

**Lowest**

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What about Patients at Moderate Risk for Thromboembolism (like our example)?

- **Recommendation:**

- There is NO recommendation!

- “In patients with a MHV, AF or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is based on an assessment of individual patient- and surgery-related factors.”
What about other practice guidelines?


“Although the use of bridging anticoagulation therapy in high-risk patients is considered the standard of care…it remains controversial.”

“The results of an ongoing trial (BRIDGE) of the use of bridging therapy in high-risk patients are awaited.”

“Our approach to bridging therapy is consistent with published (ACCP) guidelines.”

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1. Recent studies and clinical guidelines do not give us the answer that BRIDGE will provide.

2. Recent studies, including randomized trial of bridging for pacemakers does not make BRIDGE less relevant.

3. New oral anticoagulants (replacing warfarin) do not make BRIDGE less relevant...in fact, make BRIDGE more relevant!

4. Warfarin use will remain...so will the need to decide if bridging is needed!
Do recent studies answer the question: “To Bridge or not to Bridge?”

- Meta–analysis of cohort studies (no randomized trials)
- warfarin–treated patients who needed an elective surgery/procedure:
  
  3,493 patients were bridged  
  1,361 patients were not bridged

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists Systematic Review and Meta–Analysis of Bleeding and Thromboembolic Rates
Deborah Siegal, MD, MSc; Jovana Yudin, MD, BSc; Scott Kaatz, DO, MSc; James D. Douketis, MD, FRCPC; Wendy Lim, MD, MSc, FRCPC; Alex C. Spyropoulos, MD, FCCP, FRCPC.

Circulation. 2012;126:1630–1639
**Perioperative Risk for Thromboembolism: Bridging vs. No Bridging Strategies (observational studies)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bridging Events</th>
<th>Bridging Total</th>
<th>No Bridging Events</th>
<th>No Bridging Total</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniels et al., 2009</td>
<td>4</td>
<td>342</td>
<td>1</td>
<td>213</td>
<td>2.51 [0.28, 22.60]</td>
</tr>
<tr>
<td>Garcia et al., 2008</td>
<td>0</td>
<td>108</td>
<td>7</td>
<td>1185</td>
<td>0.72 [0.04, 12.76]</td>
</tr>
<tr>
<td>Jaffer et al., 2010</td>
<td>1</td>
<td>229</td>
<td>3</td>
<td>263</td>
<td>0.38 [0.04, 3.68]</td>
</tr>
<tr>
<td>Marquie et al., 2006</td>
<td>0</td>
<td>114</td>
<td>2</td>
<td>114</td>
<td>0.20 [0.01, 4.14]</td>
</tr>
<tr>
<td>McBane et al., 2010</td>
<td>10</td>
<td>514</td>
<td>6</td>
<td>261</td>
<td>0.84 [0.30, 2.35]</td>
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<tr>
<td>Tompkins et al., 2010</td>
<td>1</td>
<td>155</td>
<td>6</td>
<td>513</td>
<td>0.55 [0.07, 4.59]</td>
</tr>
<tr>
<td>Varkarakis et al., 2005</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>762</td>
<td>4.25 [0.21, 84.56]</td>
</tr>
<tr>
<td>Wysokinski et al., 2008</td>
<td>3</td>
<td>204</td>
<td>4</td>
<td>182</td>
<td>0.66 [0.15, 3.01]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1691 3493 0.80 [0.42, 1.54]

Total events 19 32

Heterogeneity: $I^2 = 0$

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No significant risk reduction for TE with heparin bridging... **BUT, major potential confounding effect**

Siegal D, et al. *Circulation* 2012;126:1630
### Perioperative Risk for Bleeding: Bridging vs. No Bridging Strategies (observational studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bridging</th>
<th></th>
<th>No bridging</th>
<th></th>
<th>Odds Ratio</th>
<th></th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>Daniels et al., 2009</td>
<td>15</td>
<td>342</td>
<td>5</td>
<td>213</td>
<td>1.91 [0.68, 5.33]</td>
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<tr>
<td>Garcia et al., 2008</td>
<td>4</td>
<td>108</td>
<td>2</td>
<td>1185</td>
<td>22.75 [4.12, 125.68]</td>
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<tr>
<td>Jaffer et al., 2010</td>
<td>13</td>
<td>229</td>
<td>3</td>
<td>263</td>
<td>5.22 [1.47, 18.54]</td>
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<tr>
<td>McBane et al., 2010</td>
<td>14</td>
<td>514</td>
<td>2</td>
<td>261</td>
<td>3.63 [0.82, 16.08]</td>
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<td></td>
</tr>
<tr>
<td>Wysokinski et al., 2008</td>
<td>6</td>
<td>204</td>
<td>4</td>
<td>182</td>
<td>1.35 [0.37, 4.86]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1397</td>
<td>2104</td>
<td>3.60 [1.52, 8.50]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: P = 52%</td>
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</table>

Bridging associated with 3- to 4-fold increase in **major** bleeding...is it an acceptable trade-off to prevent TE?

Siegal D, et al. *Circulation* 2012;126:1630
BRUISECONTROL Randomized Trial

- Patients on warfarin who need a pacemaker/ICD
- Randomized to:
  (a) continue warfarin (ensure INR <3.0 at time of procedure)
  (b) interrupt warfarin + bridge (enoxaparin 1 mg/kg BID), starting within 24 hours post-procedure

Pacemaker Pocket and Hematoma
BRUISECONTROL Randomized Trial

- Results: incidence of pacemaker hematoma
  
  continue warfarin........................3.5%
  
  interrupt warfarin + bridging......16.0% (P <0.01)

*But*...higher rates of bleeding with bridging likely because bridging started too soon after procedure!

In another study where bridging started within 24 hrs of high-bleed risk surgery (*Dunn AS, et al. JTH 2004;5:2211–8*), rate of major bleed = 20%
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4. Warfarin use will remain...so will the need to decide if bridging is needed!
Increasing use of NOACs around in USA, Canada

- NOACs have short half-lives
  - dabigatran (Pradaxa): 12–17 hours
  - rivaroxaban (Xarelto): 8–10 hours
  - apixaban (Eliquis): 7–9 hours

- This means you DO NOT need to bridge….right?

“New oral anticoagulants (Pradaxa, Xarelto, Eliquis) for AF will make this study irrelevant.”
Case Scenario No. 3

78-yr female with AF on dabigatran, 150 mg BID, scheduled for elective hip replacement with spinal anesthesia

CHADS score = 4 (prior TIA, age >75, hypertension)

CrCl = 45 mL/min (moderate renal insufficiency)
What to do pre-operatively with dabigatran?

1. Stop dabigatran 1 day before surgery
2. Stop dabigatran 4 days before surgery
3. Stop dabigatran 5 days before surgery and give therapeutic-dose LMWH bridging (enoxaparin 1 mg/kg BID) starting 3 days pre-op.
4. Stop dabigatran 5 days before surgery and administer low-dose LMWH (enoxaparin 40 mg OD) starting 3 days pre-op
Recent Evidence about NOACs and Surgery

Sub-study of the RE-LY trial: 18,000–patient randomized trial comparing dabigatran 150 mg, dabigatran 110 mg, and warfarin (target INR: 2–3) for stroke prevention in AF

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

Jeff S. Healey, MD, MSc; John Eikelboom, MD; James Douketis, MD; Lars Wallentin, MD, PhD; Jonas Oldgren, MD, PhD; Sean Yang, MSc; Ellison Themeles, BA; Hein Heidbuchle, MD; Alvaro Avezum, MD; Paul Reilly, PhD; Stuart J. Connolly, MD; Salim Yusuf, MD, DPhil; Michael Ezekowitz, MB, ChB, DPhil; on behalf of the RE-LY Investigators. Circulation. 2012;126:343–348.
# Suggestive Pre-operative Management of Dabigatran

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Estimated half-life (hrs)</th>
<th>Stop dabigatran</th>
<th>before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mL/min (mild dysfunction or normal)</td>
<td>14-17</td>
<td>higher-risk for bleeding</td>
<td>2-3 days</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min (moderate dysfunction)</td>
<td>18-24</td>
<td>4 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>&lt;30 mL/min (severe dysfunction)</td>
<td>&gt;24</td>
<td>&gt;5 days</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>

Anticoagulant Interruption in RE-LY: Patients

- 4,591 (25% of all) patients studied with first treatment interruption for surgery/procedure (8% urgent)

- Surgery/procedure types
  - 22% diagnostic (e.g., colonoscopy)
  - 10% pacemaker/ICD insertion
  - 10% dental
  - 9% cataract
  - 6% joint replacement
  - 43% other surgery (minor/major)

Healey JS, et al. Circulation 2012;126:343
Perioperative Dabigatran Management in RE-LY

- **Pre-operative**
  - last dose dabigatran given 49 hrs (range: 35–85) pre-op
  - last dose warfarin given 114 hrs (range: 87–114) pre-op

- **Post-operative**
  - anticoagulation resumed at discretion of treating physician

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Healey JS, et al. *Circulation* 2012;126:343
Anticoagulant Interruption in RE-LY: Major Bleeding

- Any surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg...... 3.8%
  - dabigatran, 150 mg...... 5.1%
  - warfarin......................... 4.6%

- Urgent surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg...... 17.8%
  - dabigatran, 150 mg...... 17.7%
  - warfarin......................... 21.6%

- Incidence of stroke or TE low and not significantly different between treatment arms

Healey JS, et al. Circulation 2012;126:343
Guidelines for Perioperative NOAC Use

European Society of Regional Anesthesia (counterpart to ASRA: American Society of Regional Anesthesia)

1. NOACs should be stopped 5 days before surgery or procedure!

2. Bridging anticoagulation with LMWH should be used in selected high-risk patients!

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Periprocedural Bridging in the RE-LY Trial

- In RE-LY, 17% of dabigatran-treated patients bridged despite short drug half-life and patients being ‘lower risk’ (mean CHADS = 2.1)
- 30–40% of dabigatran-treated patients in North America or Western Europe were bridged!
- BRIDGE is testing a concept if heparin bridging needed for short-term oral anticoagulant interruption...results also applicable to NOACs

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4. Warfarin use will remain…so will the need to decide if bridging is needed!
Warfarin will remain...

- Atrial fibrillation and well-controlled INRs
- Atrial fibrillation and concerns about NOAC use
  - no antidote if bleed occurs
  - more GI bleeding
  - impaired renal function
- What about mechanical heart valves?
NOACs for Mechanical Heart Valves?

- Phase 2 (RE-ALIGN) trial assessed dabigatran (150 mg or 300 mg BID) after mechanical aortic/mitral valve replacement vs. warfarin (INR: 2.5-3.5)
- Trial stopped (252 patients recruited) due to increased stroke/valve thrombosis and bleeding

...why more clots in mechanical heart valve patients?

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Press release, Boehringer-Ingelheim, December 12, 2012
What is the Mechanism for NOAC-associated Valve Thrombosis?

**Intrinsic Pathway**
- XIIa
- Xla
- IX
- IXa
- X
- Xa
- Thrombin (IIa)
- dabigatran

**Extrinsic Pathway (tissue factor)**
- VIIa
- TFPI

**NOACs**
- apixaban/rivaroxaban
- dabigatran

**Thrombin-Fibrin Clot**

**Contact Activation**
Why is this Relevant for the BRIDGE Trial

• Although BRIDGE excluded patients with mechanical heart valves (too difficult to randomized to placebo), the results of BRIDGE are applicable to such patients:

  1) If perioperative bridging protocol used in BRIDGE is acceptably safe, it will be used in valve patients

  2) If bridge shows no benefit, this supports NOT bridging in lower–risk valve patients (e.g., bileaflet aortic valve and no other risks)
Why we need to complete the BRIDGE trial:

1. Clinical practice guidelines are not helpful...BRIDGE will change recommendations from 2C to 1A

2. Recent bridging studies do not inform best practices...BRIDGE tells us “how to bridge”

3. Bridging is occurring in NOAC–treated patients ...BRIDGE will tell us if we need to bridge at all

4. Warfarin use will remain...so will the need for BRIDGE!
We all take part in large anticoagulant trials in patients with VTE, AF, ACS...for the most part, we know the outcome:

Is drug A as good as drug B...with possible impact on our practice

With BRIDGE...

...a challenging BUT groundbreaking trial...with definite practice-changing impact
Bridging anticoagulation...remains a foggy picture
...we can clarify it!