RCT
Potential PURL Review Form
PURL Jam Version
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PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL; BRIDGE Investigators. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Jun 22.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/26095867
3. First date published study available to readers	06/22/2015
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5. Nominated By	Other Other: Jennie Broders Jarrett
6. Institutional Affiliation of Nominator	Other Other: St. Margaret's
7. Date Nominated	06/25/2015
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9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland Other:
10. Nomination Decision Date	06/26/2015
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12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	
14. Reviewer Affiliation	Other Other: St. Margaret's
15. Date Review Due	07/07/2015
16. Abstract	Background It is uncertain whether bridging anticoagulation is necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective operation or other elective invasive procedure. We hypothesized that forgoing bridging anticoagulation would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding. Methods We performed a randomized, double-blind, placebo-controlled trial in which, after perioperative interruption of warfarin therapy, patients were randomly assigned to receive

bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. Follow-up of patients continued for 30 days after the procedure. The primary outcomes were arterial thromboembolism (stroke, systemic embolism, or transient ischemic attack) and major bleeding. Results In total, 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridginggroup and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI], -0.6 to 0.8; P=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005 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.

17. Pending PURL Review Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?

For statistical analysis, After approximately 850 patients had been enrolled, it was clear that the rate of arterial thromboembolism, as assessed by investigators who were unaware of the study-group assign- ments, was less than 0.5%, and we determined that a revised sample size of 2526 would provide at least 90% power for each primary end point. After 1720 patients were enrolled, the rate of arterial thromboembolism was 0.46%, and the bleeding rate was 2.3% in the entire population. A revised sample size of 1882 was calculated on the basis of the estimate that this would provide nearly 90% power for the two primary end points. As shown in Figure 2, we recruited 1884 patients during the period from July 2009 through Decem- ber 2014 at 108 sites in the United States and Canada; 950 patients were assigned to the placebo (no-bridging) group, and 934 patients were as- signed to receive bridging treatment with daltep- arin (bridging group).

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?

Patients were eligible to participate in the trial if they were 18 years of age or older; had chronic (permanent or paroxysmal) atrial fibrillation or flutter, confirmed by means of previous electro- cardiography or pacemaker interrogation (pa- tients with atrial fibrillation associated with valvular disease, including mitral valve disease, were eligible); had received warfarin therapy for 3 months or longer, with an international nor- malized ratio (INR) therapeutic range of 2.0 to 3.0; were undergoing an elective operation or other elective invasive procedure that required inter- ruption of warfarin therapy; and had at least one of the following CHADS2 stroke risk factors: congestive heart failure or left ventricular dys- function, hypertension, age of 75 years or older, diabetes mellitus, or previous ischemic stroke, systemic embolism, or transient ischemic attack. Patients were not eligible if they had one or more of the following: a mechanical heart valve; stroke, systemic embolism, or transient ischemic attack within the previous 12 weeks; major bleeding within the previous 6 weeks; creatinine clearance of less than 30 ml per minute; platelet count of less than 100×103 per cubic millimeter; or planned cardiac, intracranial, or intraspinal surgery.

3. Intervention(s) being investigated?

Patients were randomly assigned to receive bridging anticoagulation therapy with daltepa- rin sodium (100 IU per kilogram of body weight administered subcutaneously twice daily)from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure.

4. Comparison treatment(s), placebo, or nothing?

To receive no bridging therapy (i.e., a matching subcutaneous placebo) from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure.

5. Length of follow up?

All study outcomes were assessed by 37 days after the procedure.

Note specified end points e.g. death, cure, etc.

6. What outcome measures are used? List all that assess effectiveness.

The primary efficacy outcome was arterial thromboembolism, including stroke (ischemic or hemorrhagic), transient ischemic attack, and systemic embolism, and the primary safety outcome was major bleeding. The second- ary efficacy outcomes were acute myocardial infarction, deep-vein thrombosis, pulmonary em- bolism, and death, and the secondary safety outcome was minor bleeding.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

At 30 days after the procedure, the incidence of arterial thromboembolism was 0.4% (four events among 918 patients) in the no-bridging group and 0.3% (three events among 895 patients) in the bridging group (mean between-group difference, 0.1 per- centage points; 95% confidence interval [CI], −0.6 to 0.8; P = 0.01 for noninferiority; P = 0.73 for superiority) (Table 3). In an as-treated analy- sis, the rates of arterial thromboembolism were 0.3% (three events among 875 patients) in the no-bridging group and 0.4% (three events among 847 patients) in the bridging group (mean between-group difference, 0.0 percentage points; 95% CI, −0.7 to 0.7; P=0.006 for non- inferiority). Patients in whom arterial thrombo- embolism occurred had a mean CHADS2 score of 2.6 (range, 1 to 4), and five of the seven events occurred after a minor procedure. The median time to an arterial thromboembolism event after the procedure was 19.0 days (interquartile range, 6.0 to 23.0).

8. What are the adverse effects of intervention compared with no intervention?

Major bleeding occurred in 1.3% of the pa- tients (12 of 918) in the no-bridging group and in 3.2% (29 of 895) in the bridging group, which indicated that no bridging was superior to bridg- ing with regard to major bleeding (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005). None of the instances of major bleeding were fatal. For- going bridging was associated with a risk of minor bleeding that was significantly lower than the risk associated with bridging (12.0% vs. 20.9%, P<0.001). The median time to a major bleeding outcome after the procedure was 7.0 days (interquartile range, 4.0 to 18.0).

9. Study addresses an appropriate and clearly focused question - ***select one***

- ☒ Well covered
- ☐ Adequately addressed
- ☐ Poorly addressed
- ☐ Not applicable

Comments: Against this background, the Bridging Anti- coagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial was designed to address a simple question: in pa- tients with atrial fibrillation, is heparin bridging needed during interruption of warfarin therapy before and after an operation or other invasive procedure?

10. Random allocation to comparison groups

- ☒ Well covered
- ☒ Adequately addressed
- ☐ Poorly addressed
- ☐ Not applicable

Comments: Randomization was stratified according to study center either with the use of an interactive voice- response system with a toll-free telephone num- ber and access codes or through the Internet. The study drugs were provided in identical vials.

11. Concealed allocation to comparison groups

- ☐ Well covered
- ☒ Adequately addressed
- ☐ Poorly addressed
- ☐ Not applicable

Comments:

12. Subjects and investigators kept “blind” to comparison group allocation

- ☐ Well covered
- ☒ Adequately addressed
- ☐ Poorly addressed
- ☐ Not applicable

Comments:

12. Comparison groups are similar at the start of the trial

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: Table 1

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.

☐ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments: Perioperative management of antiplatelet therapy was left to the site investigator's discretion.

15. Were all relevant outcomes measured in a standardized, valid, and reliable way?

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

16. Are patient oriented outcomes included? If yes, what are they?

Yes, the primary outcomes were all patient oriented outcomes related to thromboembolic events. Secondary outcomes of bleeding are also patient oriented.

17. What percent dropped out, and were lost to follow up? Could this bias the results? How?

Of the 1884 patients enrolled in the trial, 71 discontinued participation and did not provide outcome data; therefore, data from 1813 patients were available for the analysis

18. Was there an intention-to-treat analysis? If not, could this bias the results? How?

yes there was

19. If a multi-site study, are results comparable for all sites?

Information from other sites was not available for determination

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?

Eisai donated the dalteparin, and University of Iowa Pharmaceuticals prepared the matching placebo. Eisai had no role in the design or con- duct of the study, the analysis of the data, or the preparation of the manuscript. The steering com- mittee vouches for the completeness and accu- racy of the data and analyses and for the fidelity of this report to the trial protocol.

21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.

Patients who are on warfarin for atrial fibrillation who are undergoing an operative procedure that would require them to be off the warfarin.

22. In what care settings might the findings apply, or not apply?

The outpatient and inpatient settings where patients are being instructed what to do with their anticoagulation related to a procedure.

23. To which clinicians or policy makers might the findings be relevant?	This would be most appropriate for the outpatient primary practitioners who would be making decisions about bridging patients perioperatively. Surgeons would also benefit this information in order to make better recommendations for their patients who are on warfarin.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions	For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year. EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.} For DynaMed, use the following style: Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}
1. DynaMed excerpts	Interruption of Therapy for Invasive Procedures: • Temporary interruption of warfarin therapy may be required in patients undergoing surgery or other invasive procedures to minimize risk of perioperative bleeding. 1004 • Assess risk of thromboembolism versus risk of perioperative bleeding to determine whether interruption of therapy is necessary. 1004 Temporary interruption of therapy usually required for major surgical or invasive procedures, but may not be necessary for minor procedures associated with a low bleeding risk (e.g., minor dental procedures, minor dermatologic procedures, cataract surgery). 1004 • If temporary interruption of warfarin necessary prior to surgery, discontinue approximately 5 days prior to procedure. 1004 May resume approximately 12–24 hours postoperatively when adequate hemostasis is achieved. 1004 • May consider bridging anticoagulation (administration of an LMWH or IV heparin during the period of warfarin interruption) in patients at particularly high risk of thromboembolism. 1004 ACCP states that bridging therapy generally unnecessary for patients other than those at highest risk for stroke and/or venous thromboembolism (e.g., patients with mechanical heart valves, atrial fibrillation, or a venous thromboembolic event with additional risk factors for venous thromboembolism). 1004
2. DynaMed citation/access date	Title. Warfarin Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 2/26/15. Accessed 7/2/15
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	May consider bridging patients on warfarin with atrial fibrillation and risk factors.
4. UpToDate excerpts	Warfarin — Warfarin blocks a vitamin K-dependent step in clotting factor production; it impairs coagulation by preventing synthesis of factors II (prothrombin), VII, IX, and X. Resolution of warfarin effect is determined by measurement of the prothrombin time, which is standardized across institutions using an international normalized ratio (PT/INR). • Discontinuation – We discontinue warfarin five days before elective surgery (ie, last dose of warfarin is given on day minus 6) and, when possible, check the PT/INR on the day before surgery (algorithm 1) [7,13,42,43]. If the INR is >1.5, we administer low dose oral vitamin K (eg, 1 to 2 mg) to hasten normalization of the PT/INR and recheck

the following day. We proceed with surgery when the INR is ≤1.4. An INR in the normal range is especially important in patients undergoing surgery associated with a high bleeding risk (eg, intracranial, spinal, urologic) or if neuraxial anesthesia is to be used. (See 'Estimating procedural bleeding risk' above and 'Neuraxial anesthesia' below.)

This timing of warfarin discontinuation is based on the biological half-life of warfarin (36 to 42 hours) and the observed time for the PT/INR to return to normal after stopping warfarin (eg, two to three days for the INR to fall to below 2.0; four to six days to normalize) [42]. Normalization of the INR may take longer in patients receiving higher-intensity anticoagulation (INR 2.5 to 3.5), and in elderly individuals [44]. Half-lives of other vitamin K antagonists also differ (eg, 8 to 11 hours for acenocoumarol; three to five days for phenprocoumon; approximately three days for fluindione). (See "Therapeutic use of warfarin and other vitamin K antagonists", section on 'Warfarin administration'.)

For a procedure that requires more rapid normalization of the INR, additional interventions may be needed to actively reverse the anticoagulant. (See 'Urgent anticoagulant reversal' below.)

This discontinuation schedule will produce a period of several days with subtherapeutic anticoagulation. As an example, it is estimated that if warfarin is withheld for five days before surgery and is restarted as soon as possible afterwards, patients would have a subtherapeutic INR for approximately eight days (four days before and four days after surgery) [13]. Thus, for patients at very high or high thromboembolic risk, bridging may be appropriate.

- Use of bridging – We generally treat individuals at very high or high risk of thromboembolism who require interruption of warfarin with a bridging agent (eg, therapeutic dose subcutaneous low molecular weight [LMW] heparin) starting three days before surgery (algorithm 1). (See 'Bridging anticoagulation' below.)

  A bridging agent may also be appropriate if there is a prolonged period during which the patient cannot take oral medications (eg, postoperative ileus).

- Restarting warfarin – We resume warfarin 12 to 24 hours after surgery, typically the evening of the day of surgery or the evening of the day after surgery, assuming there were no unexpected surgical issues that would increase bleeding risk and the patient is taking adequate oral fluids [7]. We use the same dose the patient was receiving preoperatively.

  After warfarin is restarted, it takes approximately five days for the INR to rise above 2.0, but the full anticoagulant effect of warfarin will take four to six days. Thus, we generally treat individuals at very high risk and some individuals with a high risk of thromboembolism with a heparin bridging agent during this period. (See 'Bridging anticoagulation' below.)

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Author. Gregory YH Lip, MD, FRCPE, FESC, FACC, James D Douketis, MD, FRCPC, FACP, FCCP In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: May 19, 2015.. AccessedJuly 2, 2015

6. Bottom line recommendation or summary of evidence from UpToDate
(1-2 sentences)

Bridging warfarin has a specific treatment algorithm and should be considered for patients with prolonged discontinuation or high risk of VTE.

7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	none
8. PEPID citation/access data	Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed7/2/2015
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? ☒ Yes, there is important evidence or recommendations that are missing ☐ No, this topic is current, accurate and up to date. If yes, which PEPID Topic, Title(s): perioperative mgmt of anticoagulants 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review? ☐ Yes, there is important evidence or recommendations that are missing ☒ No, this topic is current, accurate and up to date. If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
10. Other excerpts (USPSTF; other guidelines; etc.)	none
11. Citations for other excerpts	none
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	There is limited concensus on whether all patients with afib on warfarin need to be bridged for perioperative interuptions.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	Statistically there was minimal manipulation, even with the composite endpoint, where there were more strokes overall.
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7
4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.	With the emergence of the new oral anticoagulants or previous practice for not bridging would be the only limitation. Although the NOA are having a greater role in use, there continues to be a significant number of patients who need warfarin, whether for cost or renal function.
5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice	Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) ☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

that would be based on these findings represent a change from current practice?	
6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	Clearly a change in practice since the early 2000s, however there has already been a change in practice for less bridging, which this study supports.
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?	Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.	Highly applicable
9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?	Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	This can be implemmented immediately
11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?	Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.	POEM
13. In your opinion, is this a Pending PURL? Criteria for a Pending PURL: • Valid: Strong internal	Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) ☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	
14. Comments on your response in 4.13	Only reason it would not be a PURL is if practitioners were already not bridging their patients.