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Heparin bridging therapy is not necessary for patients with atrial fibrillation undergoing temporary interruption of warfarin therapy for elective invasive procedures or surgery

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ABSTRACT A critical appraisal and clinical application of Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *New Engl J Med.* Aug 2015;373(9):823-833. doi: [10.1056/NEJMoa1501035](https://doi.org/10.1056/NEJMoa1501035)

Keywords: atrial fibrillation, bridging, anti-coagulation interruption

Clinical Context

Our patient is a 70-year-old female with renal cell carcinoma of the left kidney who is being hospitalized for total left nephrectomy. She has a past medical history of morbid obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease, hyperlipidemia, atrial fibrillation. The patient has no history of smoking or alcohol use. She is a Jehovah's Witness who does not wish to receive blood products. The patient is anticoagulated with warfarin for atrial fibrillation, which was stopped five days prior to the procedure. Heparin was initiated prior to the nephrectomy and continued post-operatively for bridging therapy. As part of the Internal Medicine team, we were consulted to manage the patient's chronic medical conditions post-operatively. The patient was stabilized and ready for discharge on the second post-operative day, which was the first day of warfarin re-initiation. Enoxaparin was not covered as a discharge medication by her insurance plan. The patient was a fall risk and worked with physical therapy to ambulate post-operatively. The patient stated, "I do not want to go to rehab, I had a bad experience there before. I just want to go home." Our team wanted to determine whether or not bridging therapy with heparin was indicated for this patient as we reinitiated her warfarin therapy and prepared her for discharge to home.

Clinical Question

Should patients being anticoagulated with warfarin for atrial fibrillation undergo heparin bridging therapy after a perioperative disruption in their anticoagulation medication?

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Research Article

Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *New Engl J Med.* Aug 2015;373(9):823-833. doi: [10.1056/NEJMoa1501035](https://doi.org/10.1056/NEJMoa1501035)

Related Literature

The literature review was started with a PubMed search for articles that addressed the clinical question. Using the best match sorting feature, the search terms “anticoagulation”, “bridging”, “interruption”, and “procedure” were entered together, which yielded 102 results. The sorting feature selected the BRIDGE trial as the most relevant article, which was published in 2015 and has been cited in 38 PubMed articles since its publication.¹ Each of the 102 result articles were reviewed with a focus on study design and outcomes measured. Systematic reviews were analyzed for relevant articles, such as the review and meta-analysis by Siegal et al,² which described bleeding and thromboembolic rates in patients receiving perioperative bridging therapy. Only one of the 34 studies included in this meta-analysis used a randomized approach, rather than observational, making most studies included more susceptible to bias.³⁻⁷ Additional systematic reviews were also investigated.⁸⁻¹¹

Notable studies included the recent 2017 article by Sjögren et al., a register-based cohort study, which focused on post-warfarin cessation all-cause mortality, bleeding, and thrombosis.¹² However, in this study, the type of procedure that prompted bridging was not known, limiting the generalizability of results. Also of mention, Steinberg et al. analyzed results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), a prospective, observational registry study, and found that periprocedural bridging was associated with a higher occurrence of adverse events.¹³ Only 24 percent of study subjects underwent bridging with heparin, which limited the application of this study to the case in question. Results from the Rivaroxaban, Once Daily, Oral, Direct Factor Xa Inhibition Compared to With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), a randomized double-blind, double dummy study, described by Sherwood et al. also addressed temporary interruptions in warfarin therapy, but much like the ORBIT-AF trial, only a small portion (6%) of participants underwent bridging with heparin during anticoagulation interruption.¹⁴ Much like the ROCKET AF trial, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared an oral direct factor Xa inhibitor, apixaban, to warfarin for anticoagulation management of atrial fibrillation.¹⁵ Garcia et al. described the post-procedural outcomes of perioperative management with apixaban versus warfarin, but again, like the ROCKET AF trial, only a small portion (11.7%) of participants underwent bridging therapy during perioperative management. The decision whether or not to bridge was based on results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) open-label trial, also described by Douketis et al, which compared the effects of bridging during interruption in warfarin or dabigatran, an oral direct thrombin inhibitor, during the perioperative period.¹⁶ These RE-LY trial subset results served as a precursor to the BRIDGE trial described by Douketis, which more directly addressed the clinical question. Finally, Beyer-Westendorf et al. provided yet another notable article from the Dresden Novel Oral Anticoagulants (NOAC) trial, a prospective registry study, which provided data comparing the periprocedural management of patients on novel oral anticoagulants such as dabigatran, apixaban, or rivaroxaban, and warfarin.¹⁷ This study showed that non-bridging did not cause increased adverse outcomes, but the focus of the paper was to compare NOAC agents to warfarin, rather than the effects of bridging versus non-bridging protocols, making its results less appropriate for answering the clinical question.

The BRIDGE trial was ultimately selected for this critical appraisal because it is the only double-blind, randomized placebo-controlled trial to directly address the fundamental question of whether or not a patient with atrial fibrillation requires heparin bridging during the perioperative interruption of warfarin therapy. The BRIDGE trial studies a population with similar comorbidities to the patient in question and its method allows for the least amount of bias in comparison to other related studies.

Critical Appraisal

The Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health and managed by the Duke Clinical Research Institute. Eisai donated the dalteparin used but did not participate in the study design, data analysis, or manuscript preparation. This paper is considered Level 1 evidence by the SORT criteria.¹⁸



Randomization was stratified according to study center via an interactive telephone response system or the Internet. The characteristics of each group were very similar, indicating appropriate randomization, and the average age of participants was about 72, which is close to the age our patient. However, about 73% of participants were male and 90% were Caucasian, while our patient is an African-American female. Inclusion criteria for the study required participants be adults with chronic atrial fibrillation or flutter treated with warfarin for at least 3 months, who were undergoing an elective procedure or surgery in which warfarin therapy had to be interrupted and who also had at least one CHADS2 stroke risk factor. Our patient has hypertension and diabetes mellitus, risk factors shared by about 87% and 41% of participants, respectively. She also has a CHADS2 score of 2, similar to the average score of 2.3 amongst study participants. It is of note that few patients had higher scores of 5 or 6, though this would unlikely affect the applicability of the study to our patient, as the vast majority of trial participants had a score between 1 and 3. Our patient also did not meet any of the exclusion criteria, thus, she would qualify for this study. It is important to consider that our patient had a solid malignancy prior to her procedure. This comorbidity was shared by 7.2% of study participants in the non-bridging group and 5.6% of patients in the bridging group. The small number of participants with this co-morbidity is a notable limitation in applying the results of this trial to the patient in question, as malignancy is a contributing factor to hypercoagulability.

Our patient's procedure was considered low bleeding risk and 89.4% of participants also underwent low bleeding risk procedures. Patients were followed for 30 days postoperatively to monitor for the primary efficacy outcome of arterial thromboembolism (including stroke, transient ischemic attack, or systemic embolism) and the primary safety outcome of major bleeding (criteria for major bleeding was not specified). Adherence to the study protocol was high, with 86.5% adherence to the specified study-drug administration protocol pre-operatively and 96.5% adherence post-operatively. The post-operative adherence is more relevant to the patient in question, as the care team's main goal was to determine whether prolonging the patient's hospital stay for bridging therapy or discharging her without a heparin prescription was the safer option. Of the 950 patients assigned to the placebo group, 32 discontinued, while 39 of the 934 patients assigned to the dalteparin group discontinued participation in the study. Only three patients (0.3%) were lost to follow-up in each group, which lends confidence to the study results.

In an as-treated analysis, the study found that patients who received heparin had a comparable rate of thromboembolic events with a statistically insignificant 0.1% higher risk in the placebo group ($P=0.01$ for non-inferiority). The group who received heparin therapy was found to have a higher incidence of major bleeding at 3.2% incidence compared to 1.3% in the placebo group, which correlates with a relative risk of 0.41 for the placebo group compared to the heparin-bridged group ($P= 0.005$ for superiority). The number needed to harm (by causing major bleeding) if bridging therapy is implemented is therefore 53. Considering the associated morbidity and mortality with major bleeding events, this is a low enough number needed to harm to advise against bridging. Additionally, the study states that among the seven instances of post-procedure arterial thromboembolism, the median time to occurrence was 19 days post-procedure. Patients typically reached a therapeutic INR five to ten days after restarting warfarin. Per the study methods, once therapeutic INR was reached, bridging was discontinued. This lends further credence to the conclusion that embolism is not affected by the bridging period.

Clinical Application

With the results of this trial in mind, we considered the individual situation of our patient. She is a Jehovah's Witness who does not wish to receive blood products, which increased our concerns regarding her risk of major bleeding. Furthermore, the low-molecular-weight heparin, enoxaparin, was not covered by the patient's insurance plan. Though our patient is an African-American female and the majority of study participants were Caucasian males, she does possess the most common morbidities of BRIDGE study participants: hypertension and diabetes mellitus. It should be noted that our patient has renal cell carcinoma, whereas only 7.2% of the non-bridging group and 5.6% of the bridging group had a co-morbidity of solid malignant disease. Given that a relatively small percentage of study participants shared this co-morbidity and that a sub-group analysis of cancer patients did not occur, the applicability of the study results to our patient is somewhat limited. However, currently, stronger evidence within the literature with a specific focus on cancer patients does not exist.

The BRIDGE trial concluded that foregoing bridging therapy in a patient with non-valvular atrial fibrillation perioperatively was non-inferior to bridging with low-molecular-weight-heparin to prevent arterial thromboembolism and also decreased the risk of major bleeding. If we were to apply the results to our patient, there would still be a concern for thromboembolism, but no more than if the patient were bridged, and the



relative risk of bleeding would be less than half the risk associated with bridging, which is of importance when considering her religious preference to not receive blood products.

Our patient met the inclusion criteria for this trial, therefore, the results could be directly applied to her care. We discontinued the patient's heparin bridge therapy while continuing her previous dose of warfarin. Not only was this the most cost-effective option for our patient, but the results of this trial also show that it was the safest plan as well.

Several learning points are appreciated in evaluating this common clinical scenario:

1. Foregoing heparin therapy is found to be non-inferior to bridging therapy with low-molecular-weight heparin in preventing arterial thromboembolism in patients with non-valvular atrial fibrillation whose warfarin therapy is interrupted perioperatively.
2. Patients who receive heparin bridging therapy perioperatively are at an increased risk of major bleeding compared to those who forego bridge therapy.
3. It is critical to consistently review current literature and primary clinical research to determine the best care for patients. The results of the BRIDGE trial were published within the last three years, prior to which providers based care on clinical judgment and insufficient evidence.

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