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## A Bridge Too Far? Risks and Benefits of Perioperative Bridging Therapy

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A Bridge Too Far? Risks and Benefits of Perioperative Bridging Therapy

by

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A Scholarly Project

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### **Abstract**

The long-term use of oral anticoagulants is common among certain high-risk patient populations for the prevention of thromboembolic events such as stroke, pulmonary embolism (PE), and other systemic events. According to Garwood et al. (2017) it is estimated that 15-20% of chronically anticoagulated patients will undergo a surgery or procedure that will require anticoagulation interruption annually. During this interruption period, “bridging” anticoagulant therapy is often utilized with unfractionated heparin or low-molecular weight heparin to ensure adequate anticoagulation is achieved (Ayoub et al., 2016). However, there has been an ongoing debate whether or not the benefits of perioperative anticoagulant bridging therapy outweigh its risks.

This literature review focuses on whether or not forgoing anticoagulant bridging therapy increases the risk of postoperative thromboembolic events. It also focuses on the whether or not initiating bridging therapy places patients at a higher risk for postoperative bleeding. Finally, it focusses on the current recommendations and whether or not utilization of individualized risk assessment tools increases efficacy and safety in regards to determining appropriate bridging therapy.

The results of this literature review conclude that in low risk patients there is sufficient evidence to support the statement that non-bridging therapy is equally as efficacious to bridging therapy in the prevention of peri/postoperative thromboembolic events. There is also evidence to support the statement that traditional bridging therapy may place low risk patients at an increased risk for peri/postoperative bleeding events. Finally, there appears to be sufficient support to encourage the use of individualized risk assessment tools to help guide clinicians in their decisions to use or forgo anticoagulant bridging therapy.

## Introduction

Oral anticoagulants, most commonly vitamin K antagonists such as warfarin, are commonly used long term in patients with atrial fibrillation, a history of a mechanical heart valve, or a recent history of thromboembolic events. They are primarily used to prevent arterial and/or venous thromboembolic events such as stroke, transient ischemic attacks (TIA), deep-vein thrombosis (DVT), pulmonary embolism (PE), and other systemic embolisms. Despite newer direct oral anticoagulants, such as rivaroxaban and dabigatran, being on the market for almost a decade, vitamin K antagonists continue to lead the market as the standard treatment for chronic anticoagulation. This is especially true in patients with a history of non-valvular atrial fibrillation (Bouillon et al., 2016).

It is estimated that 15-20% of chronically anticoagulated patients will undergo an elective or emergent surgery or procedure that will require anticoagulation interruption annually (Garwood et al., 2017). Patients who are chronically anticoagulated are at a higher risk of bleeding due to the pharmacodynamics of anticoagulation medications which places them at a higher risk for a major bleeding event during surgical procedures (Lip & Douketis, 2017). During this interruption period, “bridging” anticoagulant therapy is often utilized with unfractionated heparin or low-molecular weight heparin to ensure adequate anticoagulation is achieved and to reduce the risk of a thromboembolic event perioperatively (Ayoub et al., 2016). Anticoagulant bridging medications have a different pharmacokinetic profile that makes them more easily reversible with a faster onset and offset when compared to vitamin K antagonists making them an ideal medication perioperatively.

However, there has been an ongoing debate whether or not the benefits of anticoagulant bridging therapy perioperatively outweigh the risks. This debate hinges on whether

thromboembolic events, such as a stroke or PE, caused by perioperative anticoagulant interruption posts a larger risk for patients than intra/postoperative bleeding for those who initiate bridging therapy (Douketis et al., 2015). The goal for every patient is to find a balance by reducing the risks of thromboembolic event while preventing excessive bleeding. Despite this goal the recommendations regarding initiation of perioperative bridging anticoagulants is still highly variable among experts.

### **Statement of the Problem**

Despite the universal attempt to mitigate risks for patients who are chronically anticoagulated, there is currently a lack of updated evidence-based guidelines and recommendations in regards to indications for perioperative bridging therapy. Some feel, regardless of their risk, that perioperative bridging is indicated in all chronically anticoagulated patients. While others feel the peri/postoperative risk for major bleeding events is too great to routinely subject all patients to bridging therapy risks. According to Douketis et al. (2012) “Because of the lack of evidence, practice guidelines have provided weak and inconsistent recommendations regarding the need for bridging anticoagulation”. The most recent antithrombotic guidelines come from the American College of Chest Physicians (ACCP) in 2012. Their recommendation was to approach needs for bridging anticoagulation on an individual basis taking into consideration thromboembolic and periprocedural bleeding risks. However, these current guidelines are a low-level recommendation (Level 2-C) which is reflective of the current lack of evidenced based, high-quality research and studies (Siegel et al., 2012). To date, there remains to be an anticoagulant bridging therapy that is universally accepted which tailors an individual’s thromboembolic risk factors (Pengo et al., 2009). There is

an urgent need for additional high-level studies, evidence-based guidelines, and professional recommendations to help guide clinicians to universally assess the risks and benefits for this patient population.

### **Research Questions**

Does forgoing perioperative anticoagulant bridging therapy in patients who are chronically anticoagulated place them at a higher risk for a postoperative thromboembolic event vs those patients who initiate bridging therapy?

Does initiating perioperative anticoagulant bridging therapy in patients who are chronically anticoagulated place them at a higher risk for a major intra/postoperative bleeding event vs those patients who forgo bridging therapy?

Should patients undergoing perioperative anticoagulant interruption be assessed using individualized risk assessment tools vs standardized bridging protocols to determine the need for anticoagulant bridging therapy?

### **Methodology**

A comprehensive literature review was performed utilizing CINAHL, PubMed, and SCOPUS to search and obtain pertinent, peer-reviewed medical journal articles published in English within the last 10 years. These articles were selected regarding the use of perioperative anticoagulation bridging treatment in adult patients (18 years of age or older) who are on long term anticoagulation treatment (> 3 months). Within these individual databases keywords



utilized included; perioperative, anticoagulant, interruption, adverse effects, bridging therapy, patients, thromboembolism, complications, hemorrhage, bleeding event, and time factors.

Resources were selected that either directly compared bridging therapy groups to non-bridging therapy groups, compared bleeding or thromboembolic risks, researched individualized risk assessments, or expanded on my knowledge of anticoagulant treatments, updated guidelines, or new recommendations. My searches revealed a total of 2,866 published articles. Of those studies 1,535 articles were excluded from my research for either not being published in peer-reviewed medical journals or having a publishing date greater than ten years ago.

### **Review of the Literature**

There are approximately 250,000 or more patients in the United States who are chronically anticoagulated undergoing periprocedural assessment annually (Palaniswamy & Selvaraj, 2011). Regardless, there continues to be a lack of universally accepted research and corresponding guidelines in regards to perioperative anticoagulant bridging practices. These guidelines are essential to universally reduce the risk for patients who need to undergo bridging therapy during temporary anticoagulation interruption. More research is needed to directly compare the risks and benefits of thromboembolic events, and bleeding episodes associated with anticoagulation interruption and bridging therapy.

This review of the literature focuses first on the most common pathophysiologic conditions associated with long term anticoagulant use and the pharmacology of commonly used treatments. Secondly, it compares the outcomes of peri/postoperative thromboembolic events in patients who undergo anticoagulant bridging therapy to those who forgo bridging therapy. Next, a comparison of patients who underwent anticoagulant bridging therapy compared to non-

bridging therapy and their associated bleeding risks is reviewed. Finally, a review of the current evidence-based recommendations and guidelines in regards to the pre-operative assessment of patients and their need for bridging therapy.

### **Pathophysiology and Pharmacology of Chronic Anticoagulation Therapy**

There are approximately 2.5 million people in the United States who are on long term anticoagulation therapy (Palaniswamy & Selvaraj, 2011). One of the oldest and most commonly used anticoagulant medication on the market is warfarin. Warfarin inhibits the synthesis of vitamin k-dependent coagulation factors (II, VII, IX, X, proteins C and S) which in turns reduces the formation of a thromboembolism (Bardal, Waechter, & Martin, 2011). The most common etiologies requiring the long-term use of anticoagulant medications are patients being treated for atrial fibrillation, a history of mechanical heart valve, or a history of systemic venous/arterial thromboembolic events. Of these three, atrial fibrillation is by far the most common etiology requiring chronic anticoagulation therapy. According to Lip and Douketis (2017) “Atrial fibrillation accounts for the highest percentage of patients for whom perioperative anticoagulation questions arise”.

Atrial Fibrillation is the most common sustained cardiac arrhythmia in the United States (Ayoub et al., 2016). It affects nearly 3 million people and is expected to rise to between 5.6 and 12 million people by the end of 2050 within the U.S. (Krishnamoorthy & Ortel, 2016). Of the 3 million people in the United States with atrial fibrillation, 15-20% (450,000-600,000) will undergo anticoagulation interruption annually (Garwood et al., 2017). Atrial fibrillation is a cardiac electrical disorder in which the electrical impulse generated by the upper cardiac chamber (atria) becomes disorganized and chaotic as the conduction travels to the

atrioventricular node with no discernable rate or rhythm (Lip & Douketis, 2017). This leads to an irregular and often rapid heartbeat. Due to this cardiac change patients are at an increased risk for the development of a thromboembolism which may lead to a thromboembolic event such as a stroke or pulmonary embolism.

According to the American Heart Association (AHA) and American College of Cardiology (ACC), patients with atrial fibrillation are classified based off the duration of their arrhythmia. Patients with a spontaneous termination of their arrhythmia within seven days of its onset are classified as having paroxysmal atrial fibrillation. Persistent atrial fibrillation refers to patients who have continuous arrhythmias beyond 7 days. Long-standing persistent atrial fibrillation and permanent atrial fibrillation refer to patients who have had an uninterrupted episode of arrhythmia for one year and patients whose therapeutic interventions to restore a normal rhythm have failed respectively (Lip and Douketis, 2017).

A patient's risk for thromboembolic event can be calculated based off individual risk assessments using a CHAD<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VASc risk calculator (Perrin et al., 2012). These calculators stratify an individual's risk of developing a thromboembolic event and whether or not the use of chronic anticoagulation treatment is necessary.

### **Anticoagulant Bridging Therapy: Thromboembolic Risks**

Douketis et al. (2016) performed the BRIDGE trial which was a randomized, double-blind, placebo-controlled trial where 1,884 patients were divided into two separate groups. One group comprised of 934 individuals who received bridging anticoagulation therapy with dalteparin sodium 100 IU/kg subcutaneously twice daily and the other with 950 individuals assigned to receive no bridging therapy in the form of a matching subcutaneous placebo.

Eligible patients included those who were greater than 18 years of age (mean age 71.1), had chronic atrial fibrillation or atrial flutter confirmed by EKG, and received warfarin therapy for a minimum of three months with an INR of 2.0 – 3.0. All patients were scheduled to undergo an elective procedure that required interruption of anticoagulant therapy. Finally, all patients were required to have at least one CHADS<sub>2</sub> stroke risk factor (average score 2.3). There was an extensive list of exclusion criteria that included mechanical heart valve, stroke, or transient ischemic attack within 12 weeks, or major bleed within six weeks. The study began with the discontinuation of warfarin five days prior to the day of procedure and the administration of either the placebo or dalterparin (in identical vials) three days prior. The final dose of either was given 24 hours prior to surgery. Warfarin was reinitiated for all patients at their normal dose the evening after or morning after the procedure. The re-initiation of the placebo or dalterparin was resumed 12-24 hours after if the procedure was considered low risk or 48-72 hours if considered high risk. This was continued until the patients INR was 2 or greater on at least one instance. Patients were followed weekly through phone interviews with the final encounter taking place 30-37 days postoperatively. The results from the trial for the 1,813 patients (71 discontinued participation due to consent withdrawal, lost to follow up, “other” reasons, or death) demonstrated an incidence rate for thromboembolic event of 0.4% (4 of 918) in the placebo group and 0.3% (3 of 895) in the dalterparin group (risk difference, 0.1 percentage points, 95% confidence interval [CI], -0.6 to 0.8; P=0.01 for noninferiority). The median time to a reported thromboembolic event was 19 days postoperatively. In summary, the study showed that not treating with anticoagulation bridging therapy was “non-inferior” to the use of bridging therapy in the prevention of thromboembolic events.

Krishnamoorthy and Ortel (2016) performed a review of the BRIDGE trial as well as secondary analysis from recent phase-3 randomized clinical trials. While the summary of this review agreed with the results of the BRIDGE trial they also pointed out limitations not mentioned in the trial itself. Most notably was the use of dalteparin for anticoagulant bridging therapy. This is a less commonly used medication compared to heparin or enoxaparin. They also mentioned the low rates of thromboembolic events leading to a reduction in the statistical ability to recognize a benefit associated with bridging. The review also included the RE-LY, ROCKET-AF, and ARISTOTLE trials. Through their review they concluded that the practice of anticoagulant bridging in low-moderate risk patients with atrial fibrillation may cause increased risk of bleeding events while providing little to no benefit reducing the risk of thromboembolic events. However, despite their review they did not provide any statistical analysis to support their recommendations. Their conclusion was that further research is needed to fully understand the necessity of anticoagulant bridging therapy in patients with atrial fibrillation, especially those who are at a higher thromboembolic risk.

Bouillon et al. (2016) performed a retrospective cohort study following 90,826 patients 18 years or older (mean age 72.3 years) with non-valvular atrial fibrillation who were initiated on vitamin-K antagonist treatment between January 2010 and November 2014. Exclusion criteria included but was not limited to heart valve disease, cancer, renal failure, anemia, liver disease, and dementia. Events of bleeding, systemic stroke, and systematic thromboembolic events were identified via hospital databases. Of those 90,826 patients identified, 27,147 (30%) patients were recognized as having been treated with perioperative bridging therapy (low molecular weight heparin or unfractionated heparin) seven days prior to or after vitamin-K antagonist interruption. At a subsequent one-month (30 day) follow-up the incidence of bleeding events, and stroke or

systemic embolism were compared between individuals who underwent perioperative bridging therapy to those that did not. There was a total of 151 (0.17%) episodes of ischemic stroke and systemic embolisms reported at the 1-month follow-up. There were 231 (0.31%) and 122 (0.16%) episodes reported at 2 and 3 months respectively. The results showed there was no statistically significant difference observed in the occurrence of stroke/systemic embolism between the two groups at one-month of follow-up or later (HR 0.97, 95% CI 0.68 – 1.37, P=0.841 from 0-1 months follow-up, HR 0.98, 95% CI 0.67-1.43, P=0.899 from 2-3 months of follow-up).

Ayoub et al. (2016) performed a meta-analysis of online databases including PubMed, Cochrane CENTRAL, EMBASE, Web of Science, and CINAHL through June 2015 evaluating the safety of perioperative anticoagulant bridging therapy in patients with atrial fibrillation. Utilizing the published Strengthening Meta-Analysis of Observational Studies in Epidemiology Checklist, six studies were filtered out of 511 possible articles for final review. A total of 13,808 patients were identified between the six studies; 9,556 patients fell within the no-bridging group and 4,252 were in the bridging group. The mean CHADS<sub>2</sub> scores for the non-bridging group and bridging group were 2.49 and 2.34 respectively. The results of the analysis showed no statistically significant difference in all-cause mortality (OR, 1.29; 95% CI, 0.15-11.52; P=0.82), cerebral vascular accident (OR, 0.93; 95% CI, 0.34-2.51; P=0.88), or thromboembolic events (OR, 0.72; 95% CI, 0.72-2.80; P=0.64) between the heparin bridging group and the non-bridging group at 30 days and up to 3 months. The conclusion of the study found that for patients with atrial fibrillation with a moderate risk for thromboembolic events and a CHADS<sub>2</sub> score between 2-3 there was no increase in risk for thromboembolic events or cerebral vascular accidents for

those patients opting to forgo anticoagulant bridging therapy as compared to those patients who initiated bridging therapy.

Siegal et al. (2012) performed a systematic review and meta-analysis of MEDLINE, EMBASE, and Cochrane database from 2001-2010 searching for studies where patients received perioperative heparin bridging during interruption of their vitamin K antagonists. Patients were considered to be “bridged” if they received any treatment dose of low molecular weight heparin in the perioperative bridging. Doses included 200 IU/kg/d of dalteparin or 100-120 IU/kg twice daily, enoxaparin 1.5mg/kg/d or 1mg/kg twice daily, or ardeparin 100-130 IU/kg twice daily. The final review consisted of 33 observational studies and one randomized design trial. Episodes of thromboembolic events were reported in all 34 studies. A total of 12,278 patients (> 18 years of age) were included in the study. Outcomes demonstrated thromboembolic events occurred in 73 of 7,118 patients (pooled incidence rate of 0.9%, 95% CI) who underwent anticoagulant bridging therapy and 32 of 5,160 patients (pooled incidence rate 0.6%, 95% CI) who did not undergo bridging therapy. The conclusion of the review found that the patients who were on chronic vitamin K antagonists and did not receive perioperative anticoagulant bridging treatment were at no additional risk for thromboembolic event than those who received perioperative bridging.

Ono et al. (2016) performed a retrospective data review of 3,268 patients who underwent high risk abdominal malignancy surgery over a 10-year timeframe (April 2005 – March 2015). After interruption of perioperative oral anticoagulant medication was initiated, 133 patients were initiated on low-dose heparin bridging anticoagulants (HBA) (10,000-15,000 units/day of unfractionated heparin) and 62 patients were not (non-HBA). The incidence of exogenous blood transfusion and thromboembolic events were tracked between the two groups for a 30-day period

postoperatively. A mean CHADS<sub>2</sub> scores of 2.0 was the same for both HBA and non-HBA groups. Patients with co-morbidities of atrial fibrillation, mechanical valve replacement, and history of DVT or PE were represented in both HBA and non-HBA groups. The results of the study demonstrated similar incidences between the HBA and non-HBA groups for exogenous blood transfusion (23.3% vs 19.4%,  $P = 0.587$ ) and thromboembolic events (4.1% vs 3.2%,  $P = 0.755$ ). The results demonstrate no significant rise in thromboembolic events with the non-HBA group as compared to the HBA group.

Jorgenson and Kehlet (2017) performed an observational cohort treatment study from January 2010 – November 2013 on perioperative comorbidity in patients with preoperative Vitamin K antagonist (VKA) use. Of the 13,375 patients (mean age of 68 years) undergoing unilateral hip/knee replacement, 649 patient used Vitamin K antagonists for chronic anticoagulation. Perioperative bridging was utilized in 67% of those cases (430) while only 33% had their VKA paused without bridging. Patients were followed through a 30-day postoperative follow-up. The results of their study showed no statistically significant difference between the two groups in regards to arterial thromboembolic events (0.6%, 2 in paused vs 2 bridged,  $P = 0.6$ ) or venous thromboembolic events (0.5%, 2 in paused vs 1 in bridged,  $P = 0.3$ ). The conclusion of their study demonstrated no significant difference in arterial or venous thromboembolic events between the group who received perioperative bridging and those who did not.

### **Anticoagulant Bridging Therapy: Bleeding Risks**

According to the BRIDGE trial (Douketis et al., 2016) as mentioned previously there was a statistically significant difference in bleeding events outcomes when comparing the bridged



and non- bridged groups. The occurrence of major bleeding events in the placebo group at 37 days post follow-up was 1.3% (12 of 918) compared to 3.2% (29 of 895) in the dalterparin group. The median time to major bleeding event postoperatively was approximately seven days. These results indicate that the placebo group had superior outcomes in reducing bleeding risks as compared to the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005 for superiority). In conclusion, forgoing anticoagulant bridging therapy decreased the risk of major bleeding nearly three-fold when compared to the anticoagulant bridging group.

Bouillon et al. (2016) as outlined previously showed an increase in major bleeding events at one-month post-op follow-up in the bridging group as compared to the non-bridged group (0.47% vs 0.30%; P<0.001). However, in the 2-month and 3-month follow-ups there was no difference in bleeding events between the two groups (HR 0.93; 95% CI, 0.70-1.23, P=0.593). The conclusion of this study showed patients with non-valvular atrial fibrillation who initiated anticoagulant bridging therapy had a 60% increase in major bleeding risk as compared to those who did not. This risk did not extend past the initial 30-day postoperatively follow-up, evidenced by no increased risk of bleeding events in the second and third month of follow-ups.

According to the Ayoub et al. (2016) meta-analysis as discussed previously there was a significantly reduced risk in postoperative bleeding identified in the non-bridging group as compared to the bridging group (OR, 0.41; 95% CI, 0.24-0.68; P=0.0006). According to their conclusion, patients with atrial fibrillation and low to moderate CHADS<sub>2</sub> scores who are on warfarin and require temporary interruption of chronic anticoagulation for a surgery or procedure, bridging anticoagulant therapy with unfractionated heparin or low molecular weight heparin was found to have a significantly higher risk for a major bleeding events.

Perrin et al. (2012) performed a retrospective chart review of patients who are on chronic anticoagulation therapy undergoing cardiac rhythm device surgery between March 1, 2008 and May 31, 2009. The review identified 977 patients undergoing device implantations, and of those 136 were on chronic oral anticoagulants. Additionally, seven patients were excluded due to incomplete data sets. The final 129 patients were divided into two groups based on their risk; low risk of thromboembolism (N=67), and moderate/high risk of thromboembolism (N=62). Patients were grouped based on their risk assessment according to the 2008 ACCP guidelines. The results from the review demonstrated there was an overuse in bridging therapy in patients with a low risk for thromboembolic events.

According to the Siegal et al. (2012) systematic review outlined above, an increased risk in overall bleeding events was demonstrated in bridged patients compared to non-bridged patients (5.4 vs 3.6, 95% CI). Overall bleeding episodes were reported in all 34 studies, and major bleeding events were reported in 24. Major bleeding events were described as the need for transfusion, bleeding at a critical site, >2-g/L decrease in hemoglobin, need for surgical hemostasis, fatal bleeding, or the need for hospitalization. Anticoagulant bridging therapy was associated with an overall increased risk of bleeding events in 13 studies (odds ratio, 5.40; 95% CI, 3.00-9.74) and major bleeding events in five studies (odds ratio, 3.60; 95% CI, 1.52-8.50). The conclusion of this review found that patients who are chronically anticoagulated who required temporary interruption due to surgery or procedure and receive periprocedural bridging therapy were at an increased risk for bleeding events when compared to patients who forgo bridging therapy.

Steinberg et al. (2015) performed a clinical trial of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), which is a national, community-based

registry for patients with atrial fibrillation. The review looked at patients within the registry who have been on oral anticoagulation therapy and required interruption perioperatively. A patient population of 2,803 individuals (> 18 years old with EKG demonstrated atrial fibrillation not attributed to reversible causes) with interruption of their anticoagulation were identified. Of the 2,803 interruptions, 2,138 (76%) did not use bridging therapy and 665 (24%) did. The mean CHADS<sub>2</sub> scores were similar among both groups (2.53 vs 2.34). The results of the study found that the use of anticoagulant bridging therapy in patients with atrial fibrillation resulted in significantly higher overall bleeding risks (5.0% vs 1.3%; adjusted odds ratio, 3.84; P<0.0001). The results also demonstrated a higher risk for adverse events such as myocardial infarction, stroke, major hospitalization, or death within 30-days postoperatively in patients receiving bridging therapy (13% vs 6.3%, adjusted odds ratio, 1.94, P=0.0001).

According to the Jorgenson and Kehlet (2017) observational cohort treatment study from January 2010 to November 2013 as previously outlined, there was a significantly higher rate of major bleeding events in the bridging therapy group than the non-bridge therapy group (1.2%, 1 in pauses vs 7 in bridged, P = 0.3). Their results found that due to the higher level of major bleeding events in patients who underwent anticoagulant bridging therapy additional extensive research was warranted.

### **Individualized Risk Assessments**

Palaniswamy and Selvaraj (2011) performed a stratified risk review of current periprocedural anticoagulant bridging recommendations. The review compiled eight prospective clinical trials on bridging anticoagulant therapy with a total of 4,428 patients undergoing a variety of different outpatient, low, and high-risk procedures. They tracked any major bleeding

events anywhere from 15 days to three months postoperatively. Patients were categorized based on the 2008 ACCP guidelines risk assessment including a history of mechanical heart valve, CHADS<sub>2</sub> scores, and recent thromboembolic events. The conclusion of the review showed the highest incidence rate for thromboembolic event of 3.6% at 3-month follow up and the lowest of 0.0% at 1 month. The recommendations from the study emphasized that patients with atrial fibrillation who undergo perioperative interruption of oral anticoagulation should be stratified based on their risk of thromboembolic event compared to bleeding. They recommend an individualized approach when deciding on administration of anticoagulant bridge therapy. Their recommendations lend support to the current American College of Chest Physicians (ACCP) and American Heart Association's recommendation of stratifying patients based on their individual risk factors and associated risks for thromboembolism.

Pengo et al. (2009) performed a prospective inception cohort management study following 1,262 patients with atrial fibrillation who were chronically anticoagulated undergoing invasive procedure or surgery. Each patient's oral anticoagulation was discontinued five days prior their procedure and started on low molecular weight heparin 3-4 days prior to procedure and discontinued after six days postoperatively. All patients were followed for 30 days postoperatively. The patients were divided into low thromboembolic risk (967 patients, 76.6%) and high thromboembolic risk (295 patients, 23.4%) categories. There were five reported thromboembolic events (0.4%; 95% CI, 0.1-0.9). All events occurred in the high thromboembolic risk patients. Three of the events occurred in patients who did not receive low molecular weight heparin bridging according to the assigned protocol (due to a large surgical site hematoma). The other two remaining events occurred in patients who received no bridging therapy at all. The design of the study was to establish safety and efficacy of a standardized

anticoagulant bridging management based on each patient's thromboembolic risk. The results of the study demonstrated that tailoring anticoagulant bridging therapy to a patient's thromboembolic risk index was both an effective and safe strategy.

Garwood et al. (2017) performed an extensive literature review of the most recent evidence, guidelines, and consensus statements from the last 5 years to provide an updated recommendation for the use of perioperative bridging therapy for patients with atrial fibrillation. A driving force for the updated review was the first randomized control study performed by Douketis et al. (2015) that showed treating with perioperative anticoagulant bridging therapy not only failed to reduce the risk of thromboembolic event compared to no-bridging treatment but was also associated with a three-fold increase in significant postoperative bleeding risk. Another major contribution to this article was the updated guidelines released by CHEST, AHA/ACC/HRS, ESC, and CCS. The conclusion of the review suggested the importance of risk categorization and risk/benefit assessment.

Oprea, Noto, and Halaszynski (2016) performed a risk stratification review of the most commonly used anticoagulants on the market and their discontinuation perioperatively. In regards to patients on warfarin therapy who are undergoing a procedure where perioperative anticoagulant bridging may be indicated the review broke down the management into three simple steps. The first step was to evaluate the bleeding risk through the HAS-BLED score commonly used in outpatient settings. The second step was defining the patient's thrombotic risk via the 2012 ACCP evidence-based clinical practice guidelines on perioperative management of thromboembolic events. These guidelines help stratify patients utilizing multiple categories placing them in an individualized risk assessment based on the corresponding results. The final step was evaluating the patient's HAS-BLED and CHADS<sub>2</sub> scores along with their risk

assessment to determine if anticoagulant bridging was indicated. The results of this review stressed the importance of basing treatment with anticoagulant bridging therapy on patient-specific conditions.

Perioperative bridging is a complex and often controversial topic that requires additional research. This is evidenced by many of the articles whose conclusion addressed the lack of current research and guidelines. It is important that the decision to bridge anticoagulants or not be addressed on an individual basis based on a patient's thromboembolic/bleeding risk factors including the CHADS<sub>2</sub> score and history of thromboembolic events. According to the research patients who are bridged perioperatively are placed at a higher risk for adverse bleeding events than those who forgo bridging therapy altogether in a multitude of surgical settings. In addition, there was little evidence that showed initiating bridging anticoagulants places already low risk patients at a lower risk for postoperative thromboembolic events.

### **Discussion**

According to the literature review there is statistically significant evidence to support the claim that initiating anticoagulant bridging therapy may place patients at a higher risk for intraoperative bleeding while providing little to no additional benefit in preventing thromboembolic events when compared to forgoing bridging therapy completely. The evidence found in the review of literature lends support to all three research questions asked. Many of the articles specifically highlighted the increased risk of a major bleeding events intra/postoperatively with the use of bridging anticoagulants in a variety of surgery settings. With that said, many of the articles had vastly different inclusion criteria, risk stratification, and

surgical procedure (low risk vs high risk) which makes developing a unified recommendation difficult.

**Does forgoing perioperative anticoagulant bridging therapy in patients who are chronically anticoagulated place them at a higher risk for a postoperative thromboembolic event vs those patients who initiate bridging therapy?**

According to Douketis et al. (2016) patients who underwent anticoagulant bridging therapy perioperatively were not at a lower risk for developing an intra/postoperative thromboembolic event compared to those patients who forwent bridging altogether. Of the 1,813 patients studied, four patients in the placebo group and three patients in the bridging group developed thromboembolic events within 30-37 days postoperatively. There is no statistically significant risk between these two groups. One area this study focused on that others omitted was individual risk stratification. In addition to personal history of thromboembolic events, an averaged CHADS<sub>2</sub> score was utilized to help stratify high and low risk patients. However, this study did omit high risk groups such as those with mechanical heart valves and major bleeding within six weeks. They also omitted patients who were to undergo high risk procedures including cardiac, intracranial, or intraspinal surgeries. Despite these omissions the BRIDGE study is generally regarded as a landmark trial for being one of the only double blind, randomized controlled trials comparing the use of anticoagulant bridging to non-bridging in patients with atrial fibrillation. According to Douketis et al. (2015) “The findings in our trial are consistent with those from nonrandomized comparisons of these strategies” (p. 830) in which they directly compare their trial results to that of the Siegel et al. (2012) and Steinberg et al. (2015) meta-analysis studies.

The meta-analysis study performed by Siegel et al. (2012) involved a total of 12,278 patients. However, unlike the Douketis et al. (2016) study, this meta-analysis included patients with atrial fibrillation or mechanical heart valves undergoing procedures where anticoagulant bridging was either used or not used. The results of their study showed no statistical significance in the rates of thromboembolic events between the groups. Out of the 7,118 patients started on bridging therapy, a total of 73 patients, (1.02%) had a thromboembolic event within 30 days postoperatively. Compared to the non-bridging group which had 32 thromboembolic events out of 5,160 patients (.62%). According to Siegel et al. “The risk of thromboembolic events was not significantly different in bridged and non-bridged patients”. These results are similar to the results found in many of the other studies within this review including Douketis et al. (2016), Ono et al. (2016), and Ayoub et al. (2106). The greatest strength of this study is that it is the largest systematic review of perioperative bridging therapy comparing efficacy and safety. Limitations of the study included lack of risk stratification in regards to bleeding risk, procedure type, and CHADS<sub>2</sub> scores.

According to Steinburg et al. (2015) ORBIT-AF study of 10,132 patients there was insufficient data to accurately support the use of routine bridging therapy. Of the bridging group (514) there were four (0.8%) reported episodes of thrombotic events during interruptions compared to the non-bridging groups (1,766) nine (0.5%) reported events. In addition, in a 30-day post-procedural evaluation there was one (0.2%) reported myocardial infarction and three (0.6%) strokes or other systemic embolic events report in the bridging group. In comparison, there were four (0.2%) reported myocardial infarctions and five (0.3%) reported strokes or systemic embolic events reported in the non-bridging group. Based on these results Steinburg et al. concluded that “These data do not support the use of routine bridging in anticoagulated



patients with AF, and additional data are needed to identify best practices concerning anticoagulation interruptions” (p. 493).

In addition, according to Ono et al. (2016) and their retrospective data review of 3,268 patients undergoing high risk major abdominal malignancy surgery over a 10-year time frame there was no statistically significant rise in thromboembolic events over a 30-day postoperative period when comparing bridging and non-bridging groups. This study is in contrast to many of the other studies, including Douketis et al. (2015), that only included mostly lower risk patients and minor surgeries. According to Ono et al. their results were consistent with that of the findings of the meta-analysis and prospective observational studies performed by Siegel et al. (2012), and Steinburg et al. (2015). Of note, their study analyzed patients started on the prophylactic dose (10,000-15,000 units/day) of unfractionated heparin compared to both the prophylactic and full dose analysis completed by Siegel et al.

Ayoub et al. (2016) found in their meta-analysis of 13,808 patients with atrial fibrillation undergoing periprocedural anticoagulation interruption that:

AF patients with a moderate risk for TE with CHADS<sub>2</sub> scores between 2 and 3 who required temporary interruption of warfarin for a procedure, a strategy of not bridging with heparin was similar to bridging in preventing TE and all-cause mortality, but with significantly less bleeding events (Ayoub et al., 2016, p. 2220).

Again, these results are supported by most of the above-mentioned articles. According to Ayoub et al. “Findings of the present meta-analysis are consistent with the recently published clinic trial by Douketis et al” (P. 2217).

The findings from the Douketis et al. (2015) study were further supported by the BRIDGE trial review completed by Krishnamoorthy and Ortel (2016) which found that “current

trials favor against a strategy of bridging anticoagulation for elective procedures in the majority of AF patients, low or moderate in thromboembolic risk” (p. 101). Krishnamoorthy and Ortel also agreed with the findings of Douketis et al. which concluded that the use of bridging anticoagulants showed no decrease in risk of thromboembolic events.

Further support for this research question was lent by the Bouillon et al. (2016) retrospective cohort study of 90,826 patients with non-valvular atrial fibrillation. The results from this study showed no statistically significant difference between the low molecular weight heparin bridging group and the non-bridging group in ischemic stroke or systemic embolic events at 30-days postoperatively of follow up or later. In regards to bridging therapy for patients with non-valvular atrial fibrillation Bouillon et al. (2016) states “these findings do not support the use of routine bridging in this population” (p. 9).

According to Jorgenson and Kehlet (2016) there was no statistically significant difference in arterial or venous thromboembolic events 30-days postoperatively between the bridged and non-bridged groups they studied. Perioperative bridging was used in 430 patients (67%) compared to 215 (33%) who were not bridged. There were two episodes of arterial thromboembolic events in both of the research groups. There were two episodes of venous thromboembolic events in the non-bridged group and one episode in the bridged group. Their research found similar results when compared to Douketis et al. (2015) and Ayoub et al. (2016). According to Jorgenson & Kehlet “We found similar VTE rates in bridged and paused VKA patients” (p. 59) when comparing their results to Douketis et al.

**Does initiating perioperative anticoagulant bridging therapy in patients who are chronically anticoagulated place them at a higher risk for a major intra/postoperative bleeding event vs those patients who forgo bridging therapy?**

Douketis et al. (2015) found in their randomized, double blind, placebo-controlled trial that not only was there no statistically significant change in thromboembolic events between bridged and non-bridged groups but there was a decreased risk of a major bleeding event in the non-bridged group. The incidence of major bleeding events in the non-bridged group was 1.3% compared to 3.2% in the bridging group. According to Douketis et al. “Forgoing bridging was associated with a risk of minor bleeding that was significantly lower than the risk associated with bridging” (p. 829). In addition, Douketis et al. found that “bridging conferred a risk of major bleeding that was nearly triple the risk associated with no bridging” (p. 830). These findings are consistent with the results found in Siegel et al. (2012), and Steinberg et al. (2015).

Siegel et al. (2012) found in their systematic review that patients on warfarin who received perioperative heparin bridging were at an increased risk of overall and major bleeding events compared to those non-bridged patients. In their review they found 13 studies that demonstrated an increased risk of overall bleeding events and an additional five studies that showed a significant increase in major bleeding events. According to results of their review:

Patients who receive heparin bridging appear to have an increased risk of overall and major bleeding events in the periprocedural period but a similar risk of thromboembolic events compared with patients who receive no periprocedural bridging. Thus, heparin bridging conferred a >5-fold (OR, 5.40) increased risk for overall bleeding and a >3-fold (OR, 3.60) increased risk for major bleeding, whereas the risk of thromboembolic events

was not significantly different in bridged and nonbridged patients. (Siegel et al., 2012, pp. 1635)

These results were further supported by the Douketis et al. (2015), and Steinburg et al. (2015) findings. In Douketis et al. patients were found to be at a nearly three-fold increase in risk for a major bleeding event postoperatively. According to Siegel et al. (2012) patients receiving anticoagulant bridging perioperatively were at a 3-5-fold increase in overall and major bleeding events compared to patients who received no bridging therapy. Results from both of these studies lend support to the idea that patients who receive anticoagulant bridging therapy perioperatively are at an increased risk for major bleeding events.

Steinburg et al. (2015) found similar results in their ORBIT-AF registry study.

According to their findings:

Events during interruption were relatively infrequent overall. Event rates were higher for interruptions in which bridging anticoagulants was used, including any adverse event during interruption (5.3% versus 2.8%;  $P=0.01$ ), major bleeding (3.6% versus 1.2%;  $P=0.0007$ ), bleeding hospitalizations (2.2% versus 0.7%;  $P=0.006$ ), and cardiovascular hospitalization (4.2% versus 2.2%;  $P=0.02$ ). (Steinburg et al., 2015, pp. 490)

In conclusion Steinburg et al. found that “Overall, bridging was associated with an increased risk of adverse events, including the composite of myocardial infarction, bleeding, stroke, or systemic embolism, hospitalization, or death within 30 days” (p. 490).

Further support for this research questions was provided by the Bouillon et al. (2016).

According to their research patient who received bridging therapy were at an increased risk for bleeding at a one-month follow-up compared to those who did not receive bridging therapy.

Bouillon et al. found that “After adjustment for all confounding factors (model 3), a 60%

increased risk was observed in the bridged group compared with the nonbridged counterpart during the first month of follow-up (HR=1.60; 95% CI, 1.28-2.01)” (p. 4). In conclusion they found that despite the prevalence of the practice of initiating bridging therapy, this practice actually increased the risk of bleeding events.

According to Ayoub et al. (2016) patients with atrial fibrillation receiving perioperative anticoagulant bridging with unfractionated heparin or low molecular weight heparin were at a higher risk for a major bleeding event compared to those who did not undergo bridging therapy. They found that the non-bridging group had fewer major bleeding events (OR, .41; 95% CI, .24-.68; P=.0006) and all bleeding events (OR, .44; 95% CI, .3-.65; P<.0001). Based on these findings, the conclusion of their research found that:

AF patients with a moderate risk for TE with CHADS<sub>2</sub> scores between 2 and 3 who required temporary interruption of warfarin for a procedure, a strategy of not bridging with heparin was similar to bridging in preventing TE and all-cause mortality, but with significantly less bleeding events (Ayoub et al., 2016, pp. 2220).

These findings are again consistent with the findings from Douketis et al. (2015), Steinburg et al. (2015), Bouillon et al. (2016), and Siegel et al. (2012).

Additional support for this research question was found by Perrin et al. (2012) in their retrospective chart review. They found that there was significant risk for clinical sequela, including bleeding episodes, with the use of bridging therapy. According to Perrin et al. “The overuse of bridging anticoagulation had important clinical sequela in our study resulting in three pocket hematomas and one episode of significant bleeding” (p. 1484).

Jorgensen and Kehlet (2017) found in their cohort treatment study that there was a three-times higher risk for major bleeding events in patients who received bridging therapy compared

to those who did not receive bridging therapy. In addition, they found that patients who were bridged with therapeutic doses of low molecular weight heparin were at higher risk than those bridged with prophylactic doses. This increase in bleeding risk is consistent with the findings found by Douketis et al. (2015) and Siegel et al. (2012).

**Should patients undergoing perioperative anticoagulant interruption be assessed using individualized risk assessment tools vs standardized bridging protocols to determine the need for anticoagulant bridging therapy?**

Palaniswamy and Selvaraj (2011) lend support to this research question with their stratified risk review on the necessity of warfarin interruption perioperatively and the subsequent need for bridging therapy. After reviewing the current guidelines from the ACC and AHA, in addition to many of the most recent studies on anticoagulant bridging risk, Palaniswamy and Selvaraj concluded that “Patients’ thromboembolic risk should be weighed against the bleeding risk associated with the procedure and an individualized approach should be employed in administration of bridging therapy” (P. 4) By utilizing risk factors such as CHADS<sub>2</sub> scores, and thromboembolic event patients need for anticoagulant bridging can be better analyzed and unnecessary risk mitigated.

This is further supported by the prospective inception cohort management study performed by Pengo et al. (2009). This study followed 1,262 patients with atrial fibrillation whose warfarin therapy was discontinued and perioperatively bridged utilizing low molecular weight heparin perioperatively. Their study assessed the efficacy and safety of a standardized bridging management regimens. Similar to the findings of Palaniswamy and Selvaraj (2011), the

results of Pengo et al. found that managing perioperative bridging should be tailored to a patient's individual risk factors history for optimal efficacy and risk reduction.

Oprea et al. (2016) found in their risk stratification review that patients should be treated following a simple three-step approach which individualizes every patient's risk factors in regard to perioperative anticoagulant bridging. Oprea et al. stated "Management of anticoagulation therapy in the perioperative period should be based on patient-specific conditions (renal, hepatic, cardiac) and surgery-related (trauma, cancer) issues to safely proceed with surgery and anesthetic care" (p. 597). With the inclusion of individualized risk assessments such as CHADS<sub>2</sub>, HAS-BLED, and thrombotic risk clinicians are better able to individualize patients need for perioperative anticoagulant therapy.

According to the Garwood et al. (2017) review of recent guidelines and updates, there is mounting support for the use of individualized risk factors to assess thromboembolic and bleeding risks in chronically anticoagulated patients. According to their review:

When assessing perioperative stroke risk, the American College of Chest Physicians (CHEST) guidelines, released in 2012, and the newest 2017 Expert Consensus from the American College of Cardiology (ACC) recommend stratifying a patient's thromboembolic risk into low (less than 5% annual risk), moderate (5-10% annual risk), and high (more than 10% annual risk) (Garwood et al., 2017, pp. 713).

The article outlines the importance of including CHADS<sub>2</sub> (or CHA<sub>2</sub>DS<sub>2</sub>-VASc), HAS-BLED, and BleedMAp scores. According to Garwood et al. (2017) "Appropriate assessment and risk stratification should be used to support systematic decision making in light of emerging evidence" (p. 723). This recommendation is further supported by Oprea et al. (2016), and Palaniswamy and Selvaraj (2011).

### **Applicability to Clinical Practice**

This literature review has brought an array of information together that can be applied to current clinical practice. In regards to the efficacy of perioperative anticoagulant bridging therapy and the prevention of arterial/venous thromboembolic events the evidence is certainly lacking. Many of the articles reviewed stressed the lack of statistically significant evidence showing improved outcomes in regards to thromboembolic event prevention in patients who are bridged. In fact, many of the articles went as far as to say that forgoing bridging therapy is in fact non-inferior to bridging therapy in regards to thromboembolic prevention. However, it is important to note that many of the studies only applied these results to low risk patients with an average CHADS2 score of 1-3. Also, many of these studies omitted patients who had mechanical heart valves, recent thromboembolic events, and higher risk surgeries.

In regards to bleeding risks for patients undergoing anticoagulant bridging therapy the evidence seems pretty clear. Almost every study that compared bridging therapy to non-bridging therapy found there was a higher risk associated with major bleeding events in those patients who underwent bridging therapy. Many of the articles reviewed showed an estimated three-fold increase in major bleeding risks within 30 days postoperatively. However, with that being said, there were also discrepancies between the studies regarding the type of bridging medication, dosing (prophylactic vs therapeutic), surgical procedures, and concurrent use of other antiplatelet and antithrombotic medications.

Unfortunately, for practice recommendations moving forward, there isn't enough information to provide a black and white clinical guideline as stated by many of the articles. Currently there are very few randomized control studies directly comparing the use of



perioperative bridging and non-bridging therapies. The ones that are available have omitted many of the higher risk patients leaving recommendations for only those patients classified as low-moderate risk.

However, there is a growing trend many of the articles supported with the use of individualized risk stratification when deciding on perioperative bridging vs non-bridging. These risk calculators have grown in popularity recently and have gathered support from some of the largest organizations and guidelines available today. Calculators such as the CHADS<sub>2</sub> and HAS-BLED scores were utilized in many of studies and the current evidence-based guidelines (ACCP, AHA).

The evidence from this literature review has shown that in low risk patients (CHADS<sub>2</sub> score 1-3, no history of mechanical heart valve, no recent history of thromboembolic event within 6 months) who are on chronic anticoagulant therapy and requiring temporary interruption there is evidence to support that forgoing bridging therapy may be non-inferior to bridging therapy in the prevention of thromboembolic events. There is also evidence to support that bridging therapy may place patients at a higher risk for postoperative bleeding events. Finally, there appears to be sufficient evidence to support the use of individualized risk assessment tools to calculate a patients thromboembolic and bleeding risks to help guide clinicians in their decisions to use or forgo anticoagulant bridging therapy.

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