Efficacy and Safety of Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation Undergoing Elective Surgical Procedures: A Meta-analysis

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Objective: The study objective was to determine if peri-operative bridging anticoagulation in patients with atrial fibrillation is beneficial or harmful.

Design: Systematic review and meta-analysis.

Setting: Inpatient or in-hospital setting.

Participants: Adults with atrial fibrillation having a CHADS2 score >1 undergoing elective surgical procedure on anticoagulation.

Methods: A systemic search of multiple databases (Cochrane, Medline, PubMed) was performed regarding studies conducted on efficacy and safety of perioperative bridging anticoagulation in patients with atrial fibrillation. Studies identified were reviewed by two authors individually before inclusion. The results were then pooled using Review Manager to determine the combined effect. Stroke/systemic embolism was considered as the primary efficacy outcome. Major bleeding was the primary safety outcome.

Results: The systematic search revealed 108 potential articles. The full texts of 28 articles were retrieved for assessment of eligibility. After full text review, 25 articles were excluded. Three articles met inclusion criteria. No significant difference in stroke/systemic embolism with bridging anticoagulation was noted (risk ratio, 1.25-95% confidence interval [CI], 0.55–2.85). Bridging was associated with significantly higher risk of major bleeding (risk ratio, 3.29-95% CI, 2.25–4.81).

Conclusion: An individualized approach is required when initiating peri-operative bridging anticoagulation. There is certainly a higher risk of bleeding with bridging anticoagulation and no difference in stroke/systemic embolism. However, the results cannot be extrapolated to patients who have valvular atrial fibrillation or CHADS2 score of 5 or greater.

Keywords: Bridging; Atrial fibrillation; Perioperative anticoagulation; Stroke; Systemic embolism and bleeding

Atrial fibrillation (AF) is a rising health concern, being the most common arrhythmia,¹ and its prevalence is expected to be 5.6 million by the year 2050 in the United States.² Oral anticoagulation therapy (OAC) is used to

reduce the risk of stroke and other thromboembolic events. In patients with AF on OAC who have to undergo surgical/invasive procedures, OAC therapy must be held temporarily, which may expose patients to a higher risk of thromboembolic

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events. During this period, parenteral anticoagulation in the form of low molecular weight heparin or unfractionated heparin may be used to reduce the risk of thromboembolic events, although, this bridging therapy has its own risks and benefits.³ In clinical practice, health care professionals encounter this situation quite frequently. There are few guidelines available in this regard,^{4,5} and there still appears to be a lack of evidence. Siengal et al⁶ discussed the role of bridging anticoagulation, but their study included patients not only with AF but with other indications for anticoagulation including mechanical heart valves, venous thromboembolism, and thrombotic states.⁶ We present a meta-analysis of randomized and observational studies to assess evidence for safety and efficacy of perioperative bridging in patients with AF.

The objectives of this study were to determine the efficacy and safety of peri-operative anticoagulation with anticoagulation in adults with AF having a CHADS₂ of >1 undergoing elective surgical procedure when compared to a similar population not undergoing peri-operative bridging. Only one study included CHA₂DS₂Vasc Score.⁷

Methods

Data Sources and Search Strategy

This systematic review and meta-analysis was reported according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.⁸ A systematic search of Medline (Ovid), Cochrane Central Register for Controlled Trials, and PubMed was performed from database inception through January 2019. Initial keywords utilized to perform searches were atrial fibrillation; stroke; anticoagulation; perioperative bridging; bridging; and elective surgical procedure. Medical terms (MeSH) search bar was used to identify keywords available in Medline, PubMed, and Cochrane registry. They were then combined using AND/OR. To search for grey literature and unpublished articles, we used the aforementioned keywords to perform a search in www.clinicaltrials.gov. Once the search was performed, the citations were exported to EndNote X7.5 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania) Reference Manager and duplicates were removed.

Study Selection and Data Extraction

Two authors (MUS, AKP) independently screened citations revealed after the search. If there were any disagreements, a third review author (JL) was asked to arbitrate. Studies were included if they comprised adults with AF having a CHADS₂ score of >1 undergoing an elective surgical procedure on vitamin K antagonist or non-vitamin K antagonist oral anticoagulants (NOAC). Studies that included patients admitted for emergent surgery, having a mechanical heart valve, or stroke/systemic embolism/transient ischemic attack (TIA) within 12 weeks were excluded, as this patient population is considered high risk for perioperative thromboembolism.⁵

A data collection form was created in Microsoft word and was shared among the review authors. Data regarding study characteristics, intervention, comparison, and outcomes were documented on the form (Supplementary Tables 1-3, available online). Two authors (MUS, AKP) independently extracted outcome data on a standardized data extraction tool. Any disagreements were resolved by discussion. One author (MUS) transferred data into Review Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark).

Outcomes

The primary intervention was perioperative bridging anticoagulation in patients with AF undergoing elective surgery. Arterial thromboembolism (stroke, systemic embolism, or TIA) was considered as the primary efficacy outcome. Major bleeding (gastrointestinal bleeding, intracranial bleeding, bleeding from other sites) was the primary safety outcome.

Risk of Bias

Risk of bias for each study was assessed by two authors independently using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.⁹ Any disagreements were resolved by discussion. For randomized control trials (RCTs), Cochrane risk of bias tools for RCTs was utilized (Supplementary Table 4, available online). For cohort studies, Scottish Intercollegiate Guidelines Network (SIGN) methodology was utilized to assess the risk of bias (Supplementary Table 5, available online). Each potential source of bias was graded as high, low, or unclear.

Figure 1. PRISMA flow diagram

Statistical Analysis

The statistical analyses were undertaken using Review Manager (RevMan). Outcomes from each study were pooled and compared using a random-effects (RE) model to adjust for between study variance. The treatment effect was reported as odds ratio (OR) and 95% confidence interval (CI). The I^2 -statistic was quantified to measure heterogeneity with values >25%, 50%, and 75% consistent with low, moderate, and high degrees of heterogeneity, respectively.¹⁰ Statistical significance was reached when P values were < .05. To further adjust the heterogeneity between the studies, the inverse variance heterogeneity (IVhet) estimator was implemented using MetaXL version 5.3. When compared to random effects model estimator, IVhet model has shown a lower observed variance regardless of heterogeneity.

Results

Baseline Demographics

After the search, 108 potential articles were found. A PRISMA flow diagram (Figure 1) is included for details. After removal of duplicates, 103 articles were screened. There were 75 studies not pertaining to bridging anticoagulation that were excluded after initial screening. The full texts of 28 articles were retrieved for assessment of eligibility, and 25 articles were excluded after full-text review. Among the excluded 25 articles, 19 studies were review articles, 2 studies included patients with mechanical valves, and 4 studies looked at the safety and efficacy of anticoagulation in patients undergoing radiofrequency catheter ablation of AF. There were three articles selected to perform the systematic review and meta-analysis.^{7,11,12}

This review identified 1,899 patients who were provided peri-operative bridging anticoagulation, and 4,406 patients who did

not receive peri-operative anticoagulation. Among the three studies, two were randomized controlled trials,^{7,11} and one was an observational study.¹² Two studies were published in 2015,^{7,11} and one study was published in 2008.¹² All three trials were conducted in the United States, and the baseline characteristics were consistent in all three. The mean age of the participants in the bridging arm ranged between 71.1 and 73.0 years, whereas the mean age range in the non-bridging arm was 71.8 and 74 years. The mean CHADS₂ score was 2.25 in the bridging arm and 2.1 in the non-bridging arm. Warfarin was the OAC used by the selected population in two studies, but one study included patients both on warfarin and dabigatran.⁷ All studies used low molecular weight heparin and heparin for bridging anticoagulation.

A risk of bias evaluation was performed using the Cochrane risk of bias tool (Supplementary Table 4, available online) for randomized trials^{7,11} and the SIGN tool (Supplementary Table 5, available online) for observational studies.¹² All three studies reported a low risk of bias overall (Figure 2). The participants, personnel, and outcomes assessment were blinded in all studies, suggesting low risk of performance and detection bias. Similarly, incomplete outcome data or selective reporting were not observed in the three included studies, decreasing the risk of attrition and reporting bias. The risk of selection bias was noted to be high in the study conducted by Wysokinski et al,¹² as the method of allocation concealment was not reported.

Arterial Thromboembolism

When comparing bridging anticoagulation with no bridging in patients with AF undergoing an elective surgical procedure, all three included studies in the meta-analysis individually did not show any statistically significant difference in risk of stroke and systemic embolism.

Pooled result of these three studies showed no difference in reducing stroke and/or systemic embolism when comparing bridging anticoagulation with no-bridging (OR 1.25 [0.55–2.85], $P = .60$; Figure 3). The result did not differ when we excluded the subgroup of patients in the Douketis et al⁷ RELY trial sub-study who were on dabigatran for perioperative anticoagulation instead of warfarin (OR 1.09 [0.42 – 2.85], $P = .86$; Figure 4). No variation was noted between the trials as indicated by low I^2 value of 0%.

The pooled result of the three studies using IVhet model was similar to RE model and showed no difference in reducing stroke and/or systemic embolism when comparing bridging anticoagulation with no bridging (OR 1.25 [0.55–2.85]; Supplementary Figure 1, available online).

Major Bleeding

When reviewed individually, one study¹² did not show any statistically significant difference in major bleeding, whereas the other two studies^{7,11} showed significantly increased risk of major bleeding favoring the no bridging arm. Pooled result of

	Wysokinski et al.	Douketis et al. (RELY Trial)	Douketis et al. (Bridge Trial)
Random sequence generation (selection bias)	+	+	+
Allocation concealment (selection bias)	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+
Incomplete outcome data (attrition bias)	+	+	+
Selective reporting (reporting bias)	+	+	+
Other bias	+	+	+

Figure 2. Risk of bias summary

Figure 3. Forest plot for primary efficacy outcome

these three studies identified significant difference in major bleeding, favoring no bridging when compared to bridging anticoagulation (OR 3.29 [2.25–4.81], $P < .001$; Figure 5). The safety outcome did not differ when we excluded patients on dabigatran for perioperative anticoagulation in the RELY trial⁷ (OR 2.92 [1.58–5.40], $P < .001$; Figure 6). Low and moderate variation was noted between the trials as indicated by I^2 value of 20% and 43%, respectively. When analyzed using the IVhet model, the pooled result of the three studies was similar to the RE model and showed significantly higher major bleeding in the bridging anticoagulation group (OR 3.32 [2.28–4.84]; Supplementary Figure 2, available online).

Discussion

We reviewed three studies, but there were two oral anticoagulants (warfarin and dabigatran) used in the study by Douketis et al,⁷ hence, the analysis was performed on four subgroups/studies. The total number of patients who had their bleeding and thromboembolic risk assessed exceeded 6,000. Of these, 4,406 patients were in the no bridging arm, and 1,899 patients were in bridging arm. The study denotes that patients who underwent bridging anticoagulation had more bleeding events, which was statistically significant as compared to patients who did not undergo bridging. Also, there was no significant difference between thromboembolic events in both arms. The population studied in this meta-analysis only included patients with non-valvular atrial fibrillation. Patients with mechanical heart valves, venous thromboembolism, and severe rheumatic heart disease were excluded. In their meta-analysis, Siegal et al⁶ derived the same conclusion, but the patient population was vastly different. They included patients with venous

thromboembolism, mechanical heart valves, atrial fibrillation, and various other indications. In contrast, we included patients who were on anticoagulation primarily for non-valvular atrial fibrillation. Furthermore, our analysis only contains prospective studies. We also included in our analysis the landmark BRIDGE trial.¹¹

An individualized approach is required when deciding whether or not to initiate peri-operative bridging. Mean CHADS₂ score for the patients in the bridging and non-bridging arm (Supplementary Table 2, available online) was < 4 , which confers $< 5\%$ risk of thromboembolism per year (low risk),⁴ but in clinical practice there is a wide variation of CHADS₂ scores encountered in patients with atrial fibrillation. Only 3% of participants had CHADS₂ score of 5–6 in the BRIDGE trial; therefore, the result of this meta-analysis cannot be extrapolated to this subgroup.¹¹ Patients with high CHADS₂ score are usually the ones who benefit from bridging;⁴ hence, it is important to individualize the risk of bleeding and thromboembolism before committing or deferring bridging anticoagulation in a patient.¹³ It is also difficult to extrapolate these results to the more contemporary CHA₂DS₂Vasc scoring system, since most of the patients included in this meta-analysis were stratified using the CHADS₂ score. Chao et al¹⁴ identified that patients with a CHADS₂ score of 0 can have an annual stroke rate of 4.47% when stratified using the CHA₂DS₂VASc score. Guidance can be taken from the 2017 American College of Cardiology guidelines on peri-operative management of anticoagulation in patients with non-valvular atrial fibrillation.⁴ Patients with a CHA₂DS₂VASc score of 1–4 were labelled as low risk, and bridging anticoagulation was not indicated among this subset.

Figure 4. Forest plot for primary efficacy outcome (only warfarin)

Figure 5. Forest plot for primary safety outcome

The decision of whether or not to bridge patients with a CHADS₂/VASc of ≥ 5 was dependent on thrombotic and bleeding risk assessment of individual patients.

The studies in our analysis did not have patients who had recent venous thromboembolism or had mechanical valves, so the results are not applicable to this subset of patients who require more close monitoring and robust risk-benefit assessment. PERIOP2 (a double-blind randomized control trial of postoperative low molecular weight heparin bridging therapy versus placebo bridging therapy for patients who are at high risk for arterial thromboembolism) trial, once completed, will be able to provide more guidance in this subset of high-risk patients.¹⁵ Also, the studies in this analysis did not provide any guidance regarding the bridging anticoagulation at the time of initiation of oral anticoagulation (warfarin) in new-onset atrial fibrillation patients. The results could be extrapolated, but again, each decision must be personalized depending upon the risk factors profile of the patient. The study by Steinberg et al¹⁶ is congruent with our results, but it was not included in our analysis, as it did not meet criteria (it had patients with mechanical valves).¹⁶

NOACs are as effective as vitamin K antagonist for non-valvular atrial fibrillation.¹⁷ Dabigatran was the first NOAC to be approved by the Food and Drug Administration (FDA) in 2010 after the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) was published.¹⁸ Due to their pharmacokinetic properties, NOACs have a fast onset and offset of action, which does not usually require bridging therapy.^{13,18,19} In a subset of the RELY trial, bridging in patients

taking dabigatran was associated with three times more major bleeding (6.5% vs 1.8% OR= 3.68; 95% CI: 2.24-6.04; $P < .001$) without any statistical difference in stroke.⁷ NOAC use for bridging instead of parenteral agents is thought-provoking, but some NOACs (factor Xa inhibitors) do alter the INR level; therefore, it could represent a false coagulation status prior to surgery when used for bridging in patients with atrial fibrillation. Furthermore, use of NOAC with vitamin K antagonist would theoretically increase the risk of bleeding, although the magnitude is unknown.^{20,21} The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study demonstrated low rates of major bleeding and arterial thromboembolism in patients with atrial fibrillation when NOAC therapy is interrupted without bridging in anticipation of an elective surgery.²² NOACs have a quick on and off action, which precludes the use of bridging therapy.^{13,20}

The limitations of this meta-analysis are primarily due to the inherent limitations of the included studies. We were restricted to only three studies in this meta-analysis, due to lack of randomized and non-randomized trials on this topic. One study included in this review was non-randomized, introducing the possibility of selection and sample bias. Baseline characteristics, including baseline cardiac function and bleeding risk profile, were different as well, introducing heterogeneity. Finally, we restricted this study to PubMed, Medline (Ovid), and Cochrane databases; hence, it is possible there are other studies matching our inclusion criteria that were not included in our meta-analysis.

In conclusion, this meta-analysis provides insight regarding efficacy and safety of bridging anticoagulation during temporary

Figure 6. Forest plot for primary safety outcome (only warfarin)

interruption of OAC. The results of this meta-analysis are consistent with the individual studies, particularly the BRIDGE trial. There is more risk to bridging anticoagulation than benefit in patients with atrial fibrillation. Although the current evidence and this meta-analysis identified higher risk of major bleeding in patients who were provided bridging anticoagulation, the findings can only be applied after appropriate risk and benefit assessment. Patients with higher CHADS₂ (≥ 5) score may have a higher risk of stroke than major bleeding; hence, perioperative bridging anticoagulation may be justified in this population as indicated in 2017 American College of Cardiology and 2012 American College of Chest Physicians guidelines.^{4,5} This manuscript is neither in favor of bridging anticoagulation or against it; however, it provides data that could help to make this important decision. The decision should always be individualized after contemplating the bleeding risk versus the thromboembolic risk.

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