

REVIEW TOPIC OF THE WEEK

# Bridging Anticoagulation

## Primum Non Nocere

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### ABSTRACT

Chronic oral anticoagulation frequently requires interruption for various reasons and durations. Whether or not to bridge with heparin or other anticoagulants is a common clinical dilemma. The evidence to inform decision making is limited, making current guidelines equivocal and imprecise. Moreover, indications for anticoagulation interruption may be unclear. New observational studies and a recent large randomized trial have noted significant perioperative or periprocedural bleeding rates without reduction in thromboembolism when bridging is employed. Such bleeding may also increase morbidity and mortality. In light of these findings, physician preferences for routine bridging anticoagulation during chronic anticoagulation interruptions may be too aggressive. More randomized trials, such as PERIOP2 (A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism), will help guide periprocedural management of anticoagulation for indications such as venous thromboembolism and mechanical heart valves. In the meantime, physicians should carefully consider both the need for oral anticoagulation interruption and the practice of routine bridging when anticoagulation interruption is indicated. (J Am Coll Cardiol 2015;66:1392-403) © 2015 by the American College of Cardiology Foundation.

More than 35 million prescriptions for oral anticoagulation (OAC) are written each year in the United States (1). Conditions being treated with OAC include atrial fibrillation, mechanical heart valves, venous or arterial thromboembolism, and ventricular assist devices. In any given year, 15% to 20% of these patients will undergo an invasive procedure or surgery that interrupts their chronic OAC, putting them at increased risk for thromboembolism (TE), hemorrhage, and death (2,3). Perioperative or periprocedural (hereafter combined simply as periprocedural) anticoagulation management is a common clinical dilemma, often leading to significant adverse events. The clinical relevance of this common dilemma and the lack of definitive evidence to guide medical decision making has finally led to the conduct of pertinent clinical trials, 1 of which has been recently completed (4). However, current guidelines from the American Heart

Association, American College of Cardiology, Heart Rhythm Society, and American College of Chest Physicians have yet to incorporate the findings of this trial and remain based upon observational studies and expert opinion (5,6). Yet, the guidelines do largely agree upon 3 important principles:

1. OAC should not be interrupted for procedures with low bleeding risk.
2. Patients at highest risk for TE *without* excessive bleeding risk should consider bridging. Conversely, those at low risk for TE should not be bridged.
3. Intermediate-risk cases (Table 1) should be managed by individually considering patient- and procedure-specific risks for bleeding and TE.

Patients at low risk for TE should not create a clinical dilemma. Yet, physician surveys of periprocedural bridging preferences demonstrate that approximately 30% of physicians choose to bridge



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patients at low risk for TE due to overestimation of thrombosis risk (7-9). There is even greater heterogeneity of practice in those patients with intermediate or unclear risks of bleeding or TE. Current evidence, including the recently completed BRIDGE trial (Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) (see later discussion), suggests that periprocedural bleeding rates are significantly higher than thrombosis rates in this group (2,4,10-16).

The goal of this review is not to detail the timing, doses, or specifics of bridging anticoagulation. Rather, we will review the data available to specific questions that arise in clinical practice to better individualize decision making and reduce adverse events. We have limited the scope of the discussion to anticoagulant management. The periprocedural management of antiplatelet agents has been reviewed elsewhere (5,17).

**CONFIRMING OAC INDICATIONS**

When determining the optimal periprocedural anticoagulation strategy, a critical first step is to fully appreciate the indication for chronic OAC. In some cases, OAC may no longer be required. For example, a patient may present for a procedure who has been on warfarin for a single provoked deep vein thrombosis that occurred more than 6 months prior. In such a situation, discontinuation of OAC is most appropriate and will simplify periprocedural anticoagulation management.

In some cases, OAC is indicated for acute treatment of an existing or recent TE (i.e., in the past 3 to 6 months). Although temporary discontinuation of primary prevention OAC may be appropriate, treatment of an active thrombus should not be interrupted

if at all possible. Unless a high bleeding-risk surgery is urgently needed, it is best to postpone the procedure until TE risk is attenuated.

**AVOID OAC INTERRUPTIONS**

Periprocedural warfarin interruption remains a routine practice for many clinicians. Recent data suggest that 40% to 60% of OAC interruptions may be unnecessary (2,12,18). A 2005 survey of dermatologic surgeons revealed that 44% of them routinely interrupt OAC for dermatologic surgery—a procedure with low bleeding risk (19). Other surveys similarly reveal that 90% to 100% of physicians would interrupt OAC and even bridge patients who are undergoing low bleeding-risk procedures regardless of TE risk (7,18).

OAC should not be interrupted for patients undergoing low bleeding-risk procedures, particularly those at high risk for TE. Uninterrupted warfarin throughout the periprocedural period is not associated with elevated bleeding risk for many procedures and surgeries, especially when a lower international normalized ratio (INR) goal of 2.0 is targeted (Table 2) (11,16,18,20-25). Ironically, continuous warfarin therapy can paradoxically reduce periprocedural bleeding relative to interrupted warfarin with heparin bridging (20).

Moreover, warfarin interruption and reinitiation can be associated with an increased incidence of stroke. In 1 retrospective study, warfarin initiation more than doubled the stroke risk during the first week compared with nonanticoagulated, matched control subjects (26,27). This paradox may be due to early depletion of the vitamin K-dependent factors, proteins C and S, creating a hypercoagulable milieu.

**ABBREVIATIONS AND ACRONYMS**

- INR** = international normalized ratio
- LVAD** = left ventricular assist device
- NOAC** = novel oral anticoagulant
- OAC** = oral anticoagulation
- TE** = thromboembolism
- VTE** = venous thromboembolism

**TABLE 1 Risk Stratification for Perioperative Thromboembolism as Suggested by ACCP**

Risk Group	Indication for Anticoagulation		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High*	<ul style="list-style-type: none"> <li>• Mitral valve prosthesis</li> <li>• Cage-ball or tilting disc aortic valve prosthesis</li> <li>• CVA/TIA &lt;6 months prior</li> </ul>	<ul style="list-style-type: none"> <li>• CHADS<sub>2</sub> score 5 or 6</li> <li>• CVA/TIA &lt;3 months prior</li> <li>• Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>• VTE &lt;3 months prior</li> <li>• Severe thrombophilia†</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>• Bileaflet aortic valve and other risk factors‡</li> </ul>	<ul style="list-style-type: none"> <li>• CHADS<sub>2</sub> score 3 or 4</li> </ul>	<ul style="list-style-type: none"> <li>• VTE 3-12 months prior</li> <li>• Nonsevere thrombophilia§</li> <li>• Recurrent VTE</li> <li>• Active cancer</li> </ul>
Low	<ul style="list-style-type: none"> <li>• Bileaflet aortic valve without other risk factors</li> </ul>	<ul style="list-style-type: none"> <li>• CHADS<sub>2</sub> score 2 or less without prior CVA/TIA</li> </ul>	<ul style="list-style-type: none"> <li>• VTE &gt;12 months prior without other risk factors</li> </ul>

Data from the American College of Chest Physicians (ACCP) guidelines (5). \*A true high-risk category may be difficult to objectively define in the absence of trials demonstrating benefit of heparin bridging in such patients. †Deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities. ‡CVA risk factors include: atrial fibrillation, prior CVA/TIA, hypertension, diabetes, congestive heart failure, age >75 years. §Heterozygous factor V Leiden or prothrombin gene mutation. CHADS<sub>2</sub> = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and stroke; CVA = cerebrovascular accident; TIA = transient ischemic attack; VTE = venous thromboembolism.

**TABLE 2** Procedures Amenable to Uninterrupted Therapeutic Warfarin

Endoscopy
Biopsies
Endovascular interventions
Percutaneous coronary interventions
Cardiac electrophysiology studies and ablations
Cardiac device implantation (pacemakers, defibrillators, loop recorders)
Cataract surgery
Dermatologic surgery
Dental extractions
Epidural anesthetics and likely other interventional pain management techniques
Minor noncardiac surgeries
Total knee arthroplasty
Arthroscopic surgery

Relatively major operations may also tolerate continuation of OAC. For example, certain orthopedic surgeries may also prove tolerant to uninterrupted OAC therapy. Rhodes et al. (22) retrospectively analyzed 77 patients undergoing total knee arthroplasty; 38 patients remained on warfarin throughout the perioperative period. They found no significant difference in the rates of blood transfusion, wound complications, or reoperation between the 2 groups.

Randomized studies appear to confirm these observations. Two randomized prospective trials have been conducted to directly compare the safety and efficacy of uninterrupted warfarin versus bridging with heparin. In a 2007 study, 214 patients on OAC undergoing dental extraction were randomized to either continue warfarin or to stop warfarin and bridge with heparin (23). Interrupted warfarin *without* bridging was not studied. There were no TE events in either group, consistent with the low rate of TE seen in other studies. Importantly, nearly one-half of the patients were at presumably high TE risk, with either prosthetic valves or atrial fibrillation with valvular disease. The rate of bleeding was also similar between patients with uninterrupted warfarin versus those with heparin bridging (7.34% vs. 4.76%, respectively;  $p > 0.05$ ).

BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial), published in 2013, randomized 681 high-risk patients undergoing pacemaker or defibrillator implantation to either uninterrupted OAC or interrupted OAC with heparin bridging (20). Due to the high TE risk of the study population, there was again no arm of interrupted OAC *without* bridging. The investigators found that heparin produced more than 4× as many clinically significant pocket hematomas than in those on uninterrupted warfarin (16% vs. 3.5%;  $p < 0.001$ ).

Strokes and transient ischemic attacks occurred in 2 patients on uninterrupted warfarin (0.3%), with no statistically significant difference between the groups.

Nevertheless, in many circumstances, interruption of chronic anticoagulation will be necessary to avoid excessive procedural- or surgical-related bleeding. To justify bridging anticoagulation, the risk of TE while off of anticoagulation should be great enough to justify the bleeding risk of bridging. However, as outlined in the following text, the TE risk is generally modest and outweighed by the risk of bridging-associated bleeding.

### WHAT IS THE CLOTTING AND BLEEDING RISK IN THE PERIPROCEDURAL PERIOD?

**PERIPROCEDURAL TE IS UNCOMMON.** The actual rate of periprocedural TE for unbridged OAC interruptions is rare, estimated at approximately 0.53% from our review of over 23,000 OAC interruptions in 70 studies from 1966 to 2015 (Table 3, Figure 1A) (2,4,10-16,28). From the same database, the rate of TE for patients who are bridged is slightly higher at 0.92%. The actual rate is likely higher in the absence of bridging but is biased in these observational studies by the clinician's impression of greater TE risk that drives the decision to bridge.

Rates of bleeding and TE vary by OAC indication (Figure 1B). For atrial fibrillation, an individual's daily risk of stroke or transient ischemic attack can be approximated by dividing the annual stroke risk by 365 days. Although one might expect more thrombosis in the periprocedural period by invoking Virchow's triad, observational studies have not borne this hypothesis out. For example, in ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) (2), the periprocedural cohort observed a 0.35% 30-day stroke rate. Using the average ORBIT-AF CHA2DS2-VASc score of 4.1, corresponding to an annual stroke risk of approximately 4.2%, the calculated 30-day stroke risk is surprisingly similar at 0.35%.

For mechanical heart valves, the perioperative risk of TE is approximately 1% (11). Older studies (mostly from the 1970s and 1980s) suggested a higher incidence of perioperative TE. However, these older studies included patients with higher-risk valves, such as cage-ball and tilting disc valves, which would have been far more common in that time period (29). In a more contemporary study of 45 patients with mechanical aortic and/or mitral valves who were undergoing central nervous system surgeries between 2004 and 2012, there were no TE events during an average anticoagulation gap of 7 days (14). More

**TABLE 3 Summary of All Studies Examining Periprocedural Complications by Anticoagulation Strategy From 1966 to 2015**

Study/First Author (Ref. #)	Year Published	Study Period	Study Type	Number of Studies	Number of Cases	Thromboembolic Events			Major Bleeding			Any Bleeding		
						Bridged	Not Bridged	Total %	Bridged	Not Bridged	Total %	Bridged	Not Bridged	Total %
Dunn et al. (16)	2003	1966-2001	Systematic review	31	1,176	0.6 (1)	0.6 (6)	0.60	Unavailable	Unavailable	N/A	Unavailable	Unavailable	N/A
Siegel et al. (10)	2012	2001-2010	Meta-analysis	34	12,278	1.0 (73)*	0.6 (32)*	0.85*	3.3 (211)*	0.9 (18)*	2.7*	11.6 (833)	1.9 (100)	7.56
Steinberg et al. (2)	2015	2010-2011	Prospective cohort	1	2,280	0.8 (4)	0.5 (9)	0.57	3.6 (18)	1.2 (20)	1.7	3.7 (19)	1.8 (31)	2.19
Clark et al. (12)	2015	2006-2012	Retrospective cohort	1	1,812	0 (0)	0.2 (3)	0.17	2.2 (12)	0.2 (2)	0.8	2.7 (15)	0.2 (2)	0.94
Cavalcanti et al. (14)	2015	2004-2012	Retrospective Cohort	1	45	Unavailable	Unavailable	0.00	Unavailable	Unavailable	20.0	Unavailable	Unavailable	N/A
RE-LY (28)	2015	2005-2008	Post-hoc subgroup analysis	1	4,106	1.5 (12)	0.5 (17)	0.71	6.6 (53)	1.8 (58)	2.7	Unavailable	Unavailable	N/A
BRIDGE (4)	2015	2009-2014	Randomized controlled trial	1	1,813	0.3 (3)	0.4 (4)	0.39	3.2 (29)	1.3 (12)	2.3	24.1 (216)	13.3 (122)	18.64
Combined†	2015	2001-2015	Review	39	22,334	0.94 (93)	0.52 (65)	0.71	3.5 (323)	1.2 (110)	2.38	11.8 (1,083)	2.8 (255)	7.33

Values are n or % (n) unless otherwise indicated. \*Denominator differs from number of cases stated (12,278) due to heterogeneity of definitions and reporting of events between studies reviewed. †Dunn et al. (16) excluded from combined totals to represent the most currently relevant data.  
 RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate.

than one-third of these patients were not bridged. Of note, 20% of these patients experienced a major bleeding event.

Regarding venous thromboembolism (VTE), a recent observational study of 1,257 patients found only 6 recurrent VTE events (0.4%) during the periprocedural period (12). Of the 236 patients at moderate to high risk of recurrent VTE, there was only 1 event. Two-thirds of these patients were not bridged. No difference in recurrent VTE was detected between the bridged and nonbridged groups.

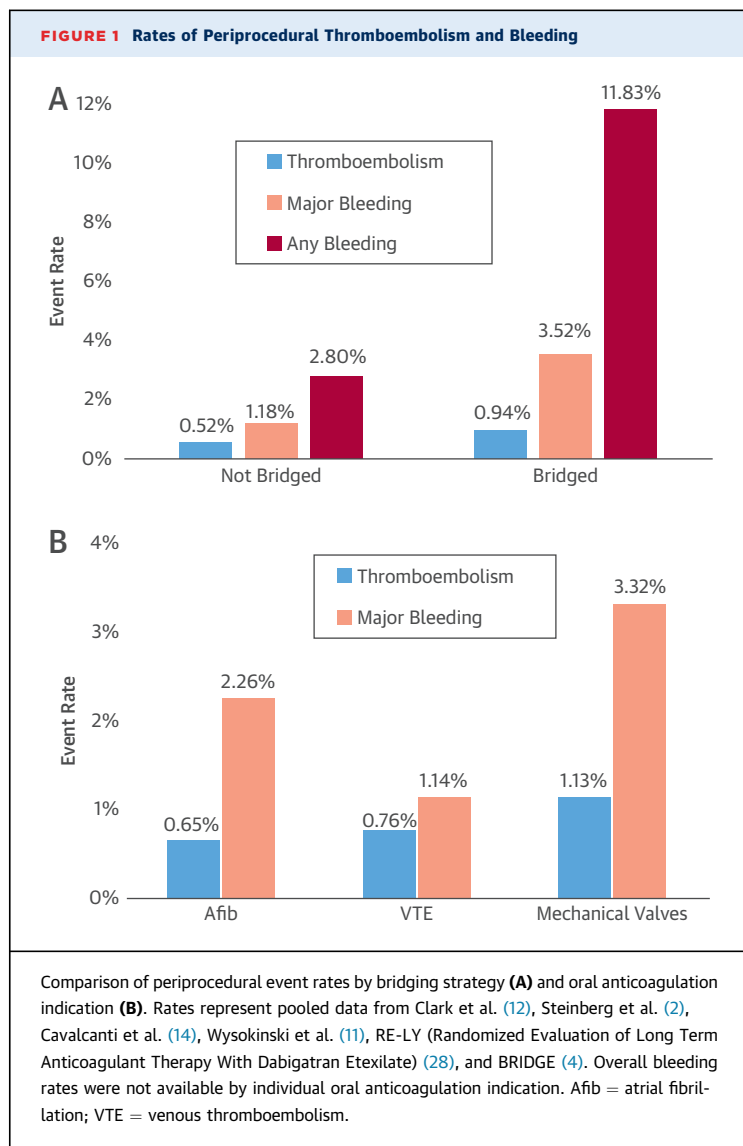
Left ventricular assist devices (LVADs) are an increasingly common indication for OAC. Management of periprocedural anticoagulation in LVAD patients is complex and consensus is lacking (30). Cumulative TE rates are surprisingly modest despite likely frequent subtherapeutic INRs (extrapolating from the experience in anticoagulation clinics). Boyle et al. (31) showed that, in 331 patients with HeartMate II LVADs (Thoratec, Pleasanton, California), the rate of TE (ischemic stroke and pump thrombosis) was 1.5% over the course of a year (31). Thrombotic events correlated with an INR <1.5, and hemorrhagic events with an INR >2.5. Meanwhile, major hemorrhage occurred 6× more frequently than TE. Another retrospective study examined patients who, for various reasons, never achieved a post-operative partial thromboplastin time >40 s after implantation of a HeartMate II. Although the stroke and pump thrombosis rates were high, subtherapeutic patients did no worse than fully anticoagulated patients. However, they experienced an absolute risk reduction of 11% fewer hemorrhagic events than their anticoagulated counterparts (32).

**BLEEDING IS MUCH MORE COMMON THAN CLOTTING.**

On average, the most recent studies demonstrate a periprocedural bleeding-to-thrombosis ratio of approximately 13:1 with bridging and 5:1 without bridging (Figure 1), suggesting that the net effect of bridging is unbalanced toward bleeding (2,10-15). In a large systematic review and meta-analysis of 34 observational studies of bridging anticoagulation, Siegal et al. (10) found an odds ratio of 3.6 (95% confidence interval: 1.52 to 8.50) for major bleeding with bridging versus nonbridging, and no significant difference in TE or mortality (Figure 2) (10). Because a systemic embolic event is often far more devastating than bleeding, an elevated bleeding-to-thrombosis ratio may be acceptable. However, a 13:1 ratio for bridging anticoagulation is likely inconsistent with the standard of primum non nocere, or “first, do no harm.”

**BLEEDING MAY BE A BIGGER THREAT THAN CLOTTING.**

Bleeding is increasingly recognized as a marker of



poor outcomes (33,34). For example, anticoagulation-related hemorrhage has been clearly associated with increased morbidity and mortality in the published medical, interventional, and surgical data and, in many cases, overwhelms the benefits of the anticoagulation (3,33,35-37). Approximately 10% of major bleeding events in patients anticoagulated for VTE ultimately end in death—ironically comparable to the mortality rate from recurrent VTE (8). In a study analyzing 3,037 atrial fibrillation patients taking OAC hospitalized at 584 centers, investigators retrospectively discovered that 14 patients died who had received heparin bridging compared with no deaths in control subjects who did not receive heparin ( $p < 0.005$ ) (34). Hospital length of stay was increased by 19.3% in association with unfractionated heparin

( $p < 0.003$ ). Also, compared with uninterrupted warfarin, bridging anticoagulation correlates with increased hospital cost ( $\$41.72 \pm \$37.81$  vs.  $\$1,114.60 \pm \$164.90$ ) (21).

Despite the evidence that: 1) TE events are rare in the periprocedural period; 2) hemorrhage is far more common than TE with bridging; and 3) there is no clear antithrombotic benefit with bridging, it remains a common and highly variable practice.

### CONTEMPORARY BRIDGING PRACTICES ARE HIGHLY VARIABLE

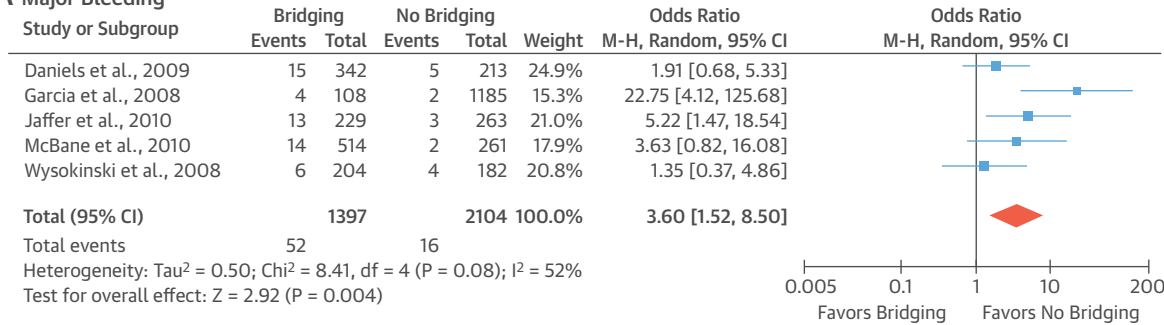
Traditional contemporary anticoagulation clinics report an average time in therapeutic range of only 65% (38). In 1 study, 23% of INR values were below 2.0 (39). Therefore, the average patient on chronic warfarin therapy spends more than 84 days/year in a subtherapeutic range. Yet, cumulative annual TE rates are modest at approximately 1% when all patients with atrial fibrillation in such programs are considered (40). It is worth noting that the length of time warfarin is interrupted for a procedure is typically  $<5$  days (13). Although it is not common practice to bridge subtherapeutic patients in the outpatient setting, many clinicians default to bridging during these short periprocedural periods—ironically, a time when patients are at greater risk of bleeding.

The threshold for bridging in current clinical practice is too low (8). Moderate- and even low-risk patients are often being bridged by default, “just to be safe.” Paradoxically, this practice is producing preventable adverse bleeding events with little benefit for thrombosis prevention. Clark et al. (12) recently described a large retrospective cohort of 1,812 procedures with chronic OAC interruption (12). They found that 73% of patients bridged for VTE were at low risk for recurrence. In addition, they may not have required OAC interruption in the first place, given that 39% of those procedures are similar to those listed in Table 2.

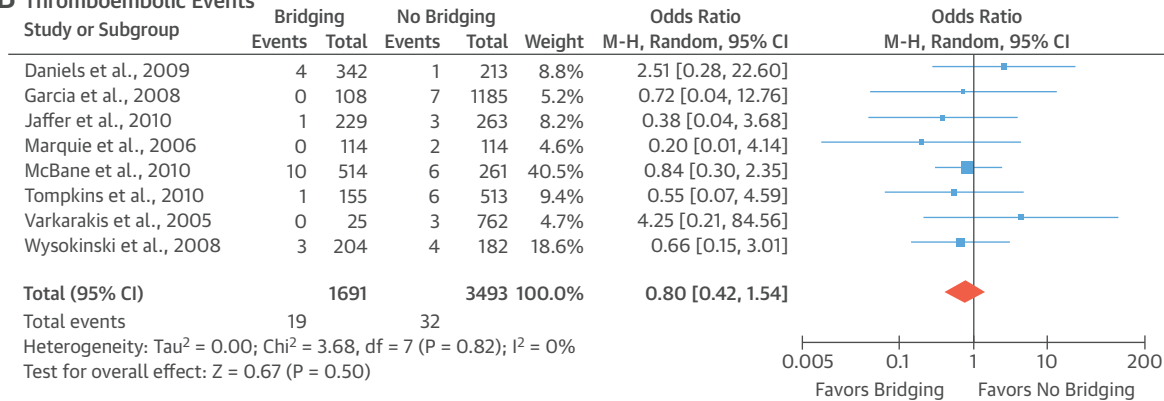
Steinberg et al. (2) analyzed the ORBIT-AF registry—a large prospective observational atrial fibrillation cohort including 2,803 OAC interruptions for various procedures. They similarly found that patients were being bridged indiscriminately, as evidenced by the similar CHA2DS2-VASc scores between the bridged and nonbridged groups. If patients’ individual bleeding risks were being considered, one would have expected the average CHA2DS2-VASc score to be higher in the bridged group. In addition, in patients whose OAC was interrupted for various procedures, bridging was associated with a 4-fold risk of bleeding (5% vs. 1.3%;

**FIGURE 2 Odds Ratios for Major Bleeding and Thromboembolic Events With Bridging**

**A Major Bleeding**



**B Thromboembolic Events**



Forest plot for major bleeding from Siegal et al. (10) demonstrates a significant odds ratio of 3.6 for patients receiving bridging anticoagulation (A). There is no significant difference in thromboembolic events between bridging and nonbridging (B). CI = confidence interval; M-H = Mantel-Haenszel. Reprinted with permission from Siegal et al. (10).

adjusted odds ratio: 3.84; p < 0.0001) with no significant difference in TE events (2).

**THE BRIDGE TRIAL**

In support of the mounting observational data, the recently published landmark BRIDGE trial now provides the most compelling evidence that routine bridging in moderate-risk patients is harmful. In the BRIDGE trial—a randomized, double-blinded, placebo-controlled noninferiority study—1,884 atrial fibrillation patients (valvular and nonvalvular) who were undergoing a procedure with planned warfarin interruption were randomized to anticoagulation bridging with the low molecular-weight heparin, dalteparin, or placebo (4). The reasons for OAC interruption were not specified, but importantly, 89.4% underwent procedures designated as “low bleeding risk.” The average CHADS<sub>2</sub> (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke) score was 2.3, making the study

population largely moderate risk for TE. The primary endpoints were arterial thromboembolism and major bleeding.

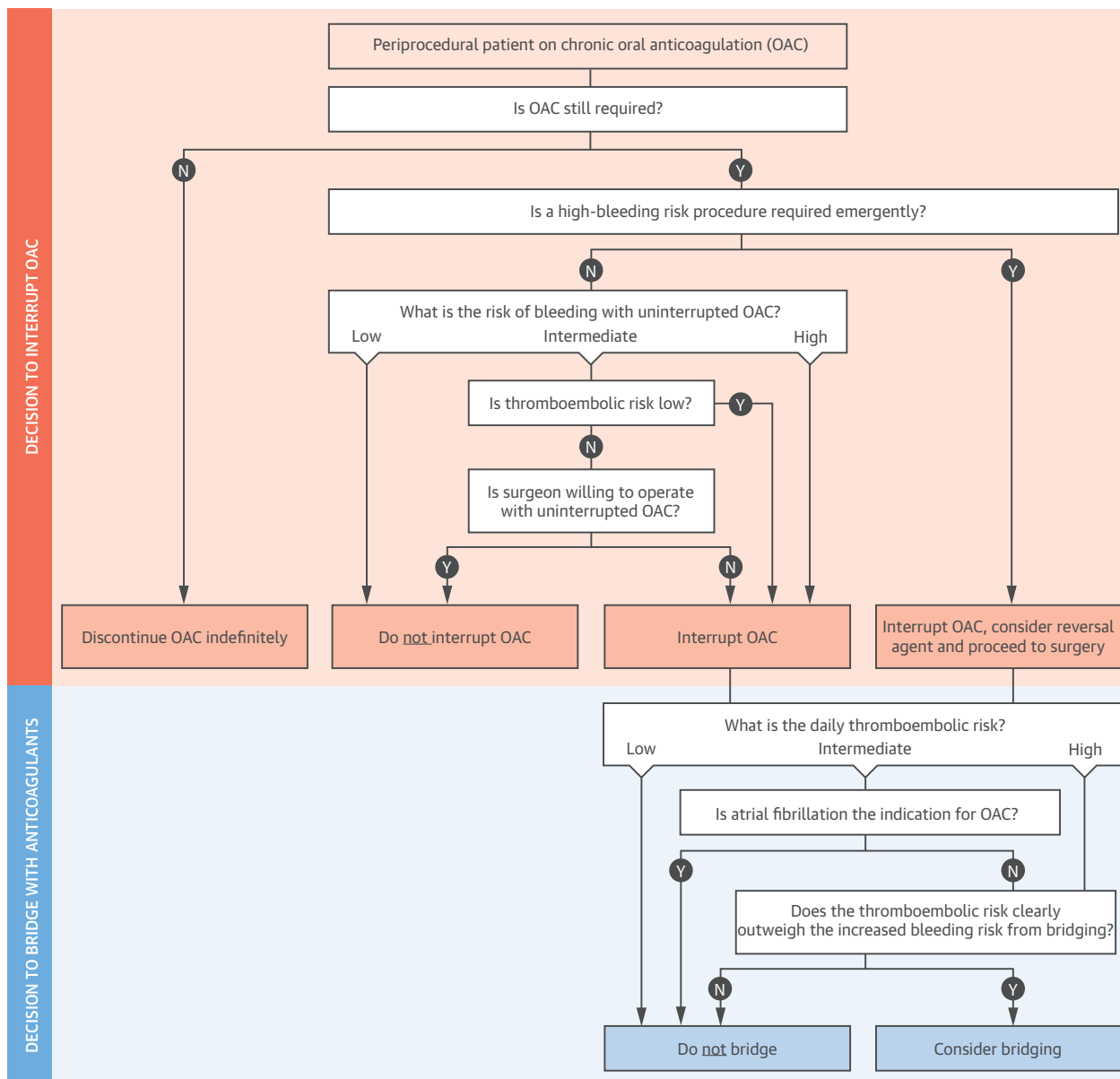
The rate of arterial TE in the placebo group was noninferior to the bridging group (0.4% vs. 0.3%; p = 0.01 for noninferiority). Major and minor bleeding in the placebo group was significantly less than in the bridging group (1.3% vs. 3.2%; p = 0.005; 12% vs. 20.9%; p = 0.001; respectively). There was no measurable difference among myocardial infarction, deep vein thrombosis, pulmonary embolism, or death.

This study confirms that no bridging is noninferior to bridging for preventing TE and is superior for reducing bleeding. The assumption that any increased bleeding caused by bridging is justified by a decrease in TE has been challenged by the BRIDGE trial. It appears that bridging in moderate-risk atrial fibrillation populations causes harm without benefit.

An important limitation of the BRIDGE trial was that the population studied was limited to patients whose anticoagulation indication was atrial



**CENTRAL ILLUSTRATION Bridging Anticoagulation: Algorithms for Periprocedural Interrupting and Bridging Anticoagulation**

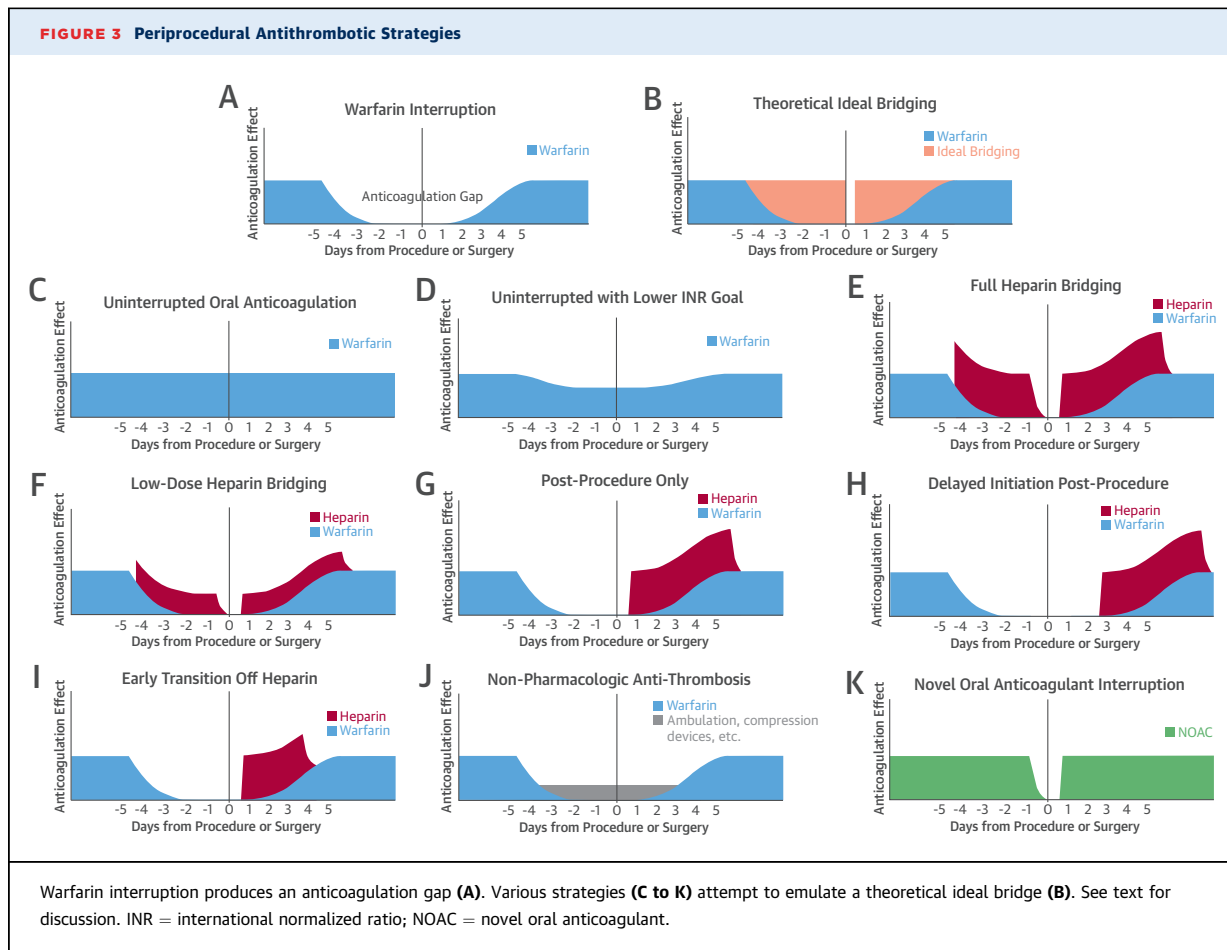


Rechenmacher, S.J. et al. J Am Coll Cardiol. 2015; 66(12):1392-403.

Decision trees for periprocedural interruption of chronic oral anticoagulation (**top**) and for periprocedural bridging anticoagulation (**bottom**). OAC = oral anticoagulation.

fibrillation and to those at predominantly intermediate risk of TE (although 16.3% had concomitant valvular disease). Extrapolation of the BRIDGE results to groups with greater TE risk, such as patients with atrial fibrillation and higher CHADS<sub>2</sub> scores,

mechanical heart valves, or recent venous or arterial thromboses, should be done cautiously. But the low arterial TE rate (0.4%) in BRIDGE patients considered to be at intermediate TE risk is reassuring. Other randomized trials are underway to address these



issues. PERIOP2 (A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism; [NCT00432796](#)) is a placebo-controlled, double-blinded, multicenter Canadian study that is randomizing moderately high-risk patients with mechanical heart valves and atrial fibrillation to dalteparin or placebo for perioperative bridging. The primary endpoint is any major TE event, including stroke, myocardial infarction, systemic embolism, valve thrombosis, VTE, or vascular death.

### A CONTEMPORARY APPROACH

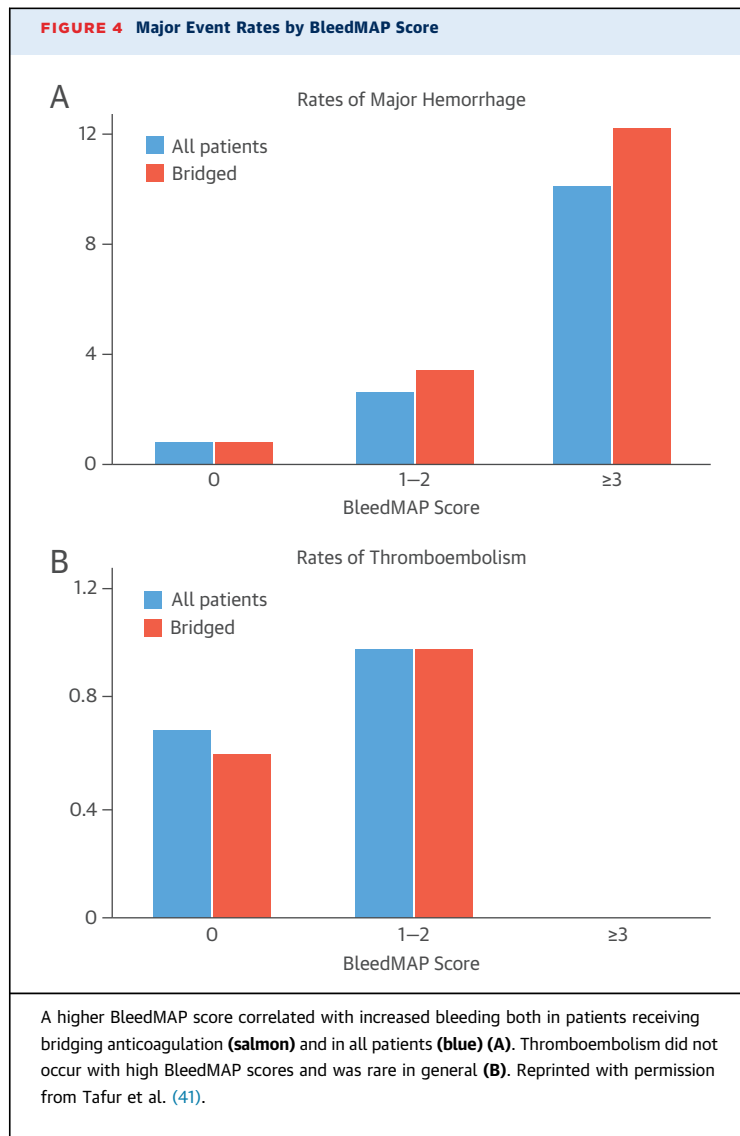
Using the cumulative available data, our approach to periprocedural anticoagulation is detailed in the following text (Central Illustration, Figure 3).

First and foremost, whenever possible, avoid interrupting OAC (Central Illustration, Figures 3C and 3D).

Candidates for uninterrupted OAC are those patients at moderate or high risk for TE and who are undergoing a reasonably low bleeding risk procedure (Table 2). To avoid unnecessary bleeding with uninterrupted OAC, also consider a lower periprocedural INR goal of 2.0 (Figure 3D).

If OAC interruption is necessary, avoid bridging patients (Figure 3A) at low or moderate risk for TE (Table 1) (5) as long as other individualized risks (i.e., existing left atrial appendage thrombus or active cancer) do not exist. Patient-specific bleeding risk should also be assessed to help guide anticoagulation decisions. One approach is to use bleeding risk calculators such as a BleedMAP score (1,27). This model was derived by retrospectively analyzing 2,484 periprocedural OAC interruptions through the Mayo Clinic Thrombophilia Center from 1997 to 2007 (41). BleedMAP assigns a point for each of the following: prior bleeding (Bleed), mechanical mitral valve (M), active cancer (A), and low platelets (P). Higher scores portend higher perioperative bleeding risk.





Conveniently, higher BleedMAP scores also correlate with lower TE rates (Figure 4).

The net clinical benefit of bridging patients at “high risk” for TE (Table 1) remains unknown and is not yet supported by clinical trial evidence. It should be noted that observational data has yet to demonstrate that bridging meaningfully reduces TE events, even in populations with high TE risk (2,10,12,16). In contrast, excessive hemorrhagic events have been well described. However, until clinical trial evidence is available, we recommend following guideline recommendations to consider individualizing bridging anticoagulation in specific high-risk patients (Table 4). For example, it might be reasonable to consider bridging in those with an unacceptably high TE risk (i.e., active or recent arterial TE or mechanical mitral

valve), with a reasonably low bleeding risk, and who require OAC interruption for more than a few days at a time (Central Illustration). Limited data suggest that mechanical valves at high risk for TE (i.e., mechanical mitral valves or tilting disc valves) may exhibit a relatively favorable bleeding-to-thrombosis profile when bridged. However, these data are retrospective (11,14). Whether or not to bridge patients with atrial fibrillation and a high CHADS<sub>2</sub> score remains unclear; PERIOP2 may help clarify this question. Although we generally support the current guidelines in high-risk patient groups, until further evidence is more definitive, we strongly encourage providers to carefully assess bleeding risk in the context of poorly defined thrombotic risk during the OAC interruption period.

When bridging is deemed necessary, more conservative bridging strategies should be entertained, such as low-dose heparin (Figure 3F) (42), post-procedure-only heparin (Figure 3G), delayed initiation of post-procedure heparin (Figure 3H), and early transitioning off of heparin as the INR approaches 2.0, rather than after (Figure 3I) (5,15,42-44). Health care providers should also consider nonpharmacological approaches (i.e., ambulation and compression stockings) to reduce thrombotic risk when OAC interruption is necessary (Figure 3J). Bleeding avoidance strategies and nonpharmacological approaches can be effective (45).

#### NOVEL ANTICOAGULANTS IN THE PERIPROCEDURAL PERIOD

Novel oral anticoagulants (NOACs) will be increasingly encountered in periprocedural scenarios. NOACs are poised to replace warfarin for the treatment of atrial fibrillation and VTE (1,46). Multiple investigators have reviewed perioperative NOACs interruptions in atrial fibrillation populations (27,28,47-49). NOAC interruptions occurred frequently in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate), ROCKET-AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) studies—25%, 33%, and 34%, respectively. Patients in these large trials did not experience increased TE or bleeding events perioperatively, whether bridged or unbridged—even those undergoing major or urgent surgical procedures (28,48). Given their pharmacokinetic similarities to low molecular-weight heparins (Figure 3K),

**TABLE 4 Bridging Recommendations and Considerations for High-Risk Patients by OAC Indication**

High-Risk OAC Indication	Thromboembolism Risk During OAC Interruption	Major Bleeding Risk	Guideline Recommendation (ACCP)	Guideline Recommendation (AHA/ACC/HRS)	Considerations Favoring <i>Not</i> Bridging
Atrial fibrillation (CHADS <sub>2</sub> ≥5)	+	+++	Bridging is favored (Grade 2C)	No specific recommendation to bridge. Individualize based on bleeding and TE risk.	<ul style="list-style-type: none"> <li>• Short OAC interruption (&lt;3-5 days)</li> <li>• Concurrent dual antiplatelet therapy</li> <li>• Active bleeding</li> <li>• High risk of major bleeding (BleedMAP score)</li> <li>• No prior TE</li> <li>• Sinus rhythm</li> </ul>
Recent VTE	+	++	Bridging is favored (Grade 2C)	N/A	<ul style="list-style-type: none"> <li>• Same as atrial fibrillation considerations</li> <li>• VTE &gt;3 months prior</li> </ul>
Recent or active arterial TE	++	++	Bridging is favored (Grade 2C)	No specific recommendation to bridge. Individualize on the basis of bleeding and TE risk.	<ul style="list-style-type: none"> <li>• Same as atrial fibrillation considerations</li> <li>• TE &gt;3 months prior</li> </ul>
Mechanical heart valve(s)	++	+++	Bridging is favored (Grade 2C)	No specific recommendation to bridge. Individualize on the basis of bleeding and TE risk.	<ul style="list-style-type: none"> <li>• Same as atrial fibrillation considerations</li> <li>• Aortic position only</li> </ul>

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AHA = American Heart Association; HRS = Heart Rhythm Society; OAC = oral anticoagulation; TE = thromboembolism; other abbreviations as in [Table 1](#).

novel anticoagulants may potentially offer a safer and simpler periprocedural management strategy than warfarin (50). In the RE-LY trial, 46% of patients treated with dabigatran were able to have their procedure within 48 h of stopping the drug, compared with only 11% of patients treated with warfarin (48).

Experience is rapidly accumulating for the periprocedural use of NOACs. However, further studies and clinical experience are needed. It is unclear if uninterrupted NOAC therapy is appropriate during even low bleeding-risk procedures. It is also unclear how soon after a procedure a NOAC can safely be restarted (47).

Clinical dilemmas presented by NOACs may become less challenging as novel reversal agents are made available in the future. A recent, non-randomized cohort study showed that idarucizumab completely reverses the anticoagulant effect of dabigatran within minutes (51). Further studies are necessary to better understand the safety and clinical outcomes associated with this medication. For now, a more conservative strategy that favors less bridging anticoagulation and, therefore, less periprocedural bleeding is favored when managing periprocedural NOACs.

## CONCLUSIONS

Periprocedural anticoagulation management is a common clinical dilemma with limited evidence (but 1 notable randomized trial) to guide our practices. Although bridging anticoagulation may be necessary for those patients at highest risk for TE, for most patients it produces excessive bleeding, longer length of hospital stay, and other significant morbidities, while providing no clear prevention of TE. Unfortunately, contemporary clinical practice, as noted in physician surveys, continues to favor interruption of OAC and the use of bridging anticoagulation. While awaiting the results of additional randomized trials, physicians should carefully reconsider the practice of routine bridging and whether periprocedural anticoagulation interruption is even necessary.

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